PEDIATRIC CLINICS OF NORTH AMERICA

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Symposium on Neoplastic Diseases

James B. Arey, M.D.
Consulting Editor

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CONTRIBUTORS

MAY ISSUE

DOROTHY H. ANDERSEN, M.D., F.A.A.P. Professor of Pathology, Columbia University College of Physicians and Surgeons; Associate Attending Pathologist, Presbyterian Hospital, New York City.

JAMES B. AREY, M.D., Ph.D. Professor of Pathology, Temple University School of Medicine; Pathologist, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania.

MARTIN BODIAN, M.D., M.R.C.P. Consultant Pathologist, The Hospital for Sick Children, London; Recognised Teacher in Pathology of the University of London, at The Institute of Child Health, London, England.

TAGUE C. CHISHOLM, M.D., F.A.C.S., F.A.C.P., F.A.A.P. Clinical Associate Professor of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota.

ROBERT S. CLELAND, M.D., F.A.A.P. Associate Professor of Pathology, University of Southern California School of Medicine; Co-pathologist, Children's Hospital, Los Angeles, California.

JOHN M. CRAIG, M.D. Assistant Professor of Pathology, Harvard Medical School; Pathologist, Children's Hospital; Research Associate, Children's Cancer Research Foundation, Boston, Massachusetts.

SAMUEL LUKENS CRESSON, M.D., F.A.C.S., F.A.A.P. Assistant Professor of Surgery, Temple University School of Medicine; Attending Surgeon, St. Christopher's Hospital for Children; Assistant Surgeon, Lankenau Hospital, Philadelphia, Pennsylvania.

ANGELO M. DI GEORGE, M.D., M.S. (Pediat.), F.A.A.P. Assistant Professor of Pediatrics, Temple University School of Medicine; Associate Attending Pediatrician and Endocrinologist, St. Christopher's Hospital for Children; Assistant Chief of Pediatrics, Philadelphia General Hospital, Blockley Division, Philadelphia, Pennsylvania.

JOHN L. EMERY, M.D., D.C.H. Honorary Lecturer in Pathology, University of Sheffield Medical School; Consultant Pathologist and Chief of the Department of Pathology, Children's Hospital, Sheffield, Yorkshire, England.

JOHN W. HOPE, M.D. Assistant Professor of Radiology, University of Pennsylvania School of Medicine and Graduate School of Medicine; Director, Department of Radiology, The Children's Hospital, Philadelphia, Pennsylvania.

JOHN A. KIRKPATRICK, Jr., M.D. Assistant Professor of Radiology (Pediatrics), Temple University School of Medicine; Radiologist, St. Christopher's Hospital for Children and Children's Heart Hospital; Attending Staff (Radiology), Veterans Administration Hospital, Philadelphia, Pennsylvania.

C. EVERETT KOOP, M.D., Sc.D. (Med.), F.A.A.P. Associate Professor of Pediatric Surgery, University of Pennsylvania School of Medicine and Graduate School of Medicine; Surgeon-in-Chief, The Children's Hospital, Philadelphia, Pennsylvania.

ISADORE LAMPE, M.D., Ph.D. Professor of Radiology, University of Michigan Medical School; Alice Crocker Lloyd Radiation Therapy Center, University of Michigan Medical Center, Ann Arbor, Michigan.

BENJAMIN H. LANDING, M.D. Assistant Professor of Pathology and Pediatrics, University of Cincinnati College of Medicine; Directing Pathologist, Children's Hospital and Children's Hospital Research Foundation, Cincinnati, Ohio.

HOWARD B. LATOURETTE, M.D. Associate Professor of Radiology, University of Michigan Medical School; Alice Crocker Lloyd Radiation Therapy Center, University of Michigan Medical Center, Ann Arbor, Michigan.

JOHN S. McGAVIC, M.D., M.S. (Surg.), F.A.C.S. Professor of Ophthalmology, Temple University School of Medicine; Professor of Clinical Ophthalmology, University of Pennsylvania Graduate School of Medicine; Attending Ophthalmologist, Temple University Medical Center, Philadelphia, and Bryn Mawr Hospital, Bryn Mawr, Pennsylvania.

FELIX A. McPARLAND, M.D. Attending Pediatric Surgeon, Minneapolis General Hospital, Minneapolis, Minnesota.

LESTER W. MARTIN, M.D. Assistant Professor of Pediatrics, University of Cincinnati College of Medicine; Director of Pediatric Surgery, Children's Hospital, Cincinnati, Ohio.

M. LOIS MURPHY, M.D. Assistant Professor of Medicine, Sloan Kettering Division (Cornell University), New York City.

FREDERICK MURTAGH, M.D., M.Sc., F.A.C.S. Assistant Professor of Neurosurgery, Temple University Medical Center; Associate Attending Neurosurgeon, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania.

KARL E. PASCHKIS, M.D. Associate Professor of Medicine and of Physiology, Jefferson Medical College; Director, Division of Endocrine and Cancer Research, Jefferson Medical College; Chief of Endocrine Clinic, Jefferson Medical College Hospital; Attending Endocrinologist, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania.

EUGENE V. PERRIN, M.D. Instructor in Pathology, Columbia University College of Physicians and Surgeons; Resident in Pathology, Babies Hospital, New York City.

GEORGE P. PILLING, IV, M.D., F.A.C.S., F.A.A.P. Associate in Surgery, Temple University School of Medicine; Associate Attending Surgeon, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania.

BERNARD J. SPENCER, M.D., F.A.C.S., F.A.C.P. Clinical Instructor in Surgery, University of Minnesota Medical School, Minneapolis, Minnesota.

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GENERAL CONSIDERATIONS ON NEOPLASMS IN EARLY LIFE

JAMES B. AREY, M.D.

Consulting Editor

BACHRACH

Cancer, including leukemia, is now the single leading cause of death from disease in children in the United States between the ages of 3 and 14 years.[8] Although the increasing importance of cancer as a cause of death in children is in part related to improved diagnoses and to the decline in death rates from infectious diseases, there is some evidence to indicate an actual as well as a relative increase in its incidence. Thus in Scotland, although the total number of deaths in children under 15 years of age fell from approximately 62,000 to 21,000 in a period of 20 years, the number of deaths from neoplasms, including leukemia, rose from 242 to 425.[4]

In the United States cancer, including leukemia, is responsible for almost 12 per cent of all deaths between the ages of 1 and 14 years.[8] Malignant neoplasms are, however, far less frequent in the pediatric age group than in the total population; among 16,565 malignant neoplasms at the Memorial Hospital in New York City only 1.7 per cent were from patients less than 15 years of age.[5]

Although cancer plays an important role as a cause of mortality in early life, it is not a frequent cause of morbidity. Even in pediatric hospital populations, where there is an obvious concentration of the more seriously ill children, admissions for cancer comprise only a small

part of the total number of patients. During the period 1924–51 only 0.66 per cent of the admissions to the James Whitcomb Riley Memorial Hospital were for malignant neoplasms, including leukemia.[3] During the 5-year period ending June 30, 1958, there were 19,363 admissions to St. Christopher's Hospital for Children. Among these were 67 infants and children with leukemia and 90 with other types of malignant neoplasms; i.e., 0.81 per cent of all admissions were for some form of cancer.

More instances of cancer are observed during the first 5 years of life than during either of the two ensuing quinquennia; 55 per cent of the leukemias observed in children are in the age period 0 to 4 years.[2] The frequency of malignant neoplasms during the first five years of life probably reflects the embryonal nature of certain of the more frequent tumors encountered in this period, e.g., Wilms' tumor and neuroblastoma. Such embryonal neoplasms tend to mimic structures normally present during active organogenesis,[1] and are obviously derived from primitive cells which have never matured. They may already be present at the time of birth,[6] but may also arise postnatally from cells which have not yet attained complete maturation.

As is true of malignant neoplasms in general, the explanation for the occurrence of these embryonal tumors in children is not apparent. Although it has frequently been assumed that they arise from embryonal rests, such potentially malignant rests are only infrequently encountered in routine postmortem studies of large numbers of infants. Moreover, even were such an origin accepted, the explanation for the malignant transformation of such rests remains obscure. It is of interest that some embryonic tissues appear to be highly sensitive to the action of certain carcinogenic agents, and that some of these agents can be transmitted to the fetus through the placenta;[3] the possibility that certain chemical agents, either of exogenous or endogenous origin, may play a role in the development of some of the embryonal neoplasms of children warrants further investigation.

The embryonal origin of certain neoplasms of early life is undoubtedly responsible for differences between these tumors and the more common malignant neoplasms encountered in adults. The rapidity of progress of many of the neoplasms of children as compared with those of adults is probably related to the growth characteristics of embryonic tissues.[7] As a result of rapid growth, the clinical manifestations of certain neoplasms in infants and children may be those of an acute infectious process, and few or none of the classic signs of malignancy encountered in adults may be observed. Except for tumors of the central nervous system and acute leukemia, malignant neoplasms in early life usually manifest themselves by the presence of an abnormal solid mass, which may attain a large size in a brief time. Characteristically, how-

ever, even large tumors are not associated with significant anemia, loss of weight or cachexia.

Although almost all types of malignant tumors have been reported before the age of puberty on one or more occasions, the common sites of origin of malignant neoplasms in early life differ sharply from those in adults. Thus the hematopoietic system, central and sympathetic nervous systems, including the eye, and the adrenal, soft tissues, bone and kidney are the common sites of origin of malignant tumors in infants and children; the common epithelial tumors of adults, e.g., carcinomas of the skin, stomach, lung, breast, and uterus, are rare in early life. Tumors of mesodermal or ectodermal (central nervous system) origin predominate in early life, and sarcomas are far more frequent than carcinomas. As might be expected, the incidence of benign tumors exceeds that of malignant ones.

Not only are the clinical manifestations, sites of origin and types of tumors different in infants and children from those commonly encountered in adults, but also the pathologic criteria of malignancy used in evaluating neoplasms in adults are not always applicable to tumors in infants and children. For example, encapsulation is commonly considered to be indicative of benignancy in a neoplasm in an adult, but the Wilms' tumor and even the neuroblastoma may be encapsulated initially. Incompletely differentiated tissues in a tumor in an adult are commonly associated with other evidences of malignancy, but such tissues in a teratoma in an infant may merely reflect incomplete differentiation of the tissues at this age, and are not of necessity indicative of a malignant neoplasm. Moreover, the incompletely differentiated tissues of certain malignant neoplasms of infancy, i.e., neuroblastomas, may on rare occasions complete their normal cycle of maturation, with resultant conversion of a neoplasm which is at least histologically malignant to one which is histologically and clinically benign; unfortunately, this is probably not a common occurrence, at least in those neuroblastomas which have grown to sufficient size so as to manifest themselves clinically. Invasion of adjoining tissues, the presence of mitotic figures and increased cellularity are all features commonly associated with malignant neoplasms in adults, but almost without exception their occurrence in hemangiomas in infants is associated with a benign clinical course. Such an active histologic appearance associated with a benign clinical course might be predicted from the nature of the infantile hemangioma, which probably represents a hamartoma rather than a true neoplasm. Hamartomas are tumor-like congenital malformations resulting from continued growth of tissues indigenous to the part, and as such they might be expected to reflect the active growth which is characteristic of early life.

Similarly, benign nevi in children commonly reveal more evidence of

activity than do those in adults, and in certain ones the histologic appearance may strongly suggest a malignant melanoma. Nevertheless, with rare exceptions, nevi in children behave in a benign manner clinically and do not require radical surgical excision.

Conversely, certain tumors in early life may appear histologically benign and yet behave clinically as malignant ones. The juvenile nasopharyngeal angiofibroma may invade adjoining tissues and may recur repeatedly, but its histologic appearance is usually that of a benign lesion; although metastases do not occur, its clinical behavior is certainly suggestive of a low grade malignant neoplasm.

This in no way lessens the importance of histologic diagnoses in the evaluation of suspected neoplasms in early life, and treatment should not be instituted until the exact nature of the mass is established by histologic examination. The interpretation of the pathologist, however, will of necessity be influenced by a knowledge of the natural course of a given neoplasm as observed in other infants and children. The final decision as to therapy is dependent not only upon the nature of the neoplasm, but also upon the clinical and, in many instances, roentgenographic appraisal of the patient. Accordingly, a variety of disciplines in medicine are represented by the contributors to the present volume, since there are many facets to the total care of an infant or child with a suspected or proved neoplasm.

That such a volume should be deemed worthy of publication is in itself indicative of the increasing importance of neoplasms as a cause of serious disease in early life. Its value, however, would be questionable had not advances in all fields of medicine appreciably improved the prognosis of certain types of malignant neoplasms encountered in infants and children. Although leukemia continues to be invariably fatal, the advances which have been made in the care of these patients now permit many of the affected children to live a normal life for months or even years. Not only is survival under such optimal conditions of importance to the patient, but also its psychologic benefits to the family may, in some instances, be incalculable. Moreover, certain neoplasms formerly considered to be almost invariably fatal may now be successfully treated in an appreciable number of instances, e.g., Wilms' tumor, neuroblastoma and certain tumors of the central nervous system. Although the prognosis remains grave, it is certainly better than that of such common cancers of adult life as carcinoma of the stomach or lung.

Although the results of therapy are still far from satisfactory, certain general principles have evolved which, with improved techniques of anesthesiology and surgery, have contributed to the more hopeful outlook for many infants and children with malignant neoplasms. It is now recognized, for example, that *every solid mass in an infant or child should be regarded as a malignant neoplasm until proved otherwise.*

Needless palpation of a suspected neoplasm should be avoided, and the mass should be removed after as brief a time as is consistent with adequate clinical evaluation and preparation of the patient for operation; usually this period need not exceed 48 hours. Treatment by other than surgical excision should not be instituted until an unequivocal diagnosis has been established by histologic study.

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2600 North Lawrence St.
Philadelphia 33, Pa.

TUMORS OF THE CENTRAL NERVOUS SYSTEM

FREDERICK MURTAGH, M.D.

Neoplasms arising within the central nervous system differ from those elsewhere in that they do not metastasize beyond the limits of the craniovertebral cavity. Medulloblastomas and certain types of ependymoma tend to seed themselves throughout the subarachnoid space and spinal canal, but generally are locally aggressive in the organ of origin. Multiple primary tumors in the central nervous system are rare.

For malignant growth anywhere in the body, early detection followed by total surgical excision remains the most effective method of treatment. This concept is based on the principle that a tumor detected in the early phase of its development can be excised beyond the limits of its local extension and eliminated before widespread, distant metastases occur. The same concept applies equally well to tumors of the central nervous system, but the basic principle differs. Generalized metastatic dissemination of the tumor is not a factor to be considered in the management. Early detection is desirable before irreversible neurologic damage has been produced by local invasion and by the devastating effects of increased intracranial pressure. Wide excision of nerve tissue around a tumor is not permissible. As much of the tumor as practicable must be removed with minimal disturbance of the surrounding normal tissue in order to preserve maximum neurologic function.

To achieve this objective, a high degree of suspicion must be maintained toward any unexplained, progressive neurologic symptom in a patient in any age group. Precise neurosurgical diagnostic studies should be used liberally for even minimal indications in order to detect possible neoplastic disease.

An increasing number of adult patients are being presented for diagnostic survey before major neurologic deficit is evident and before in-

From the Neurosurgical Service at St. Christopher's Hospital for Children and Temple University Medical Center, Philadelphia.

creased intracranial pressure is present or has progressed remarkably. Preoperative localization of intracranial neoplasms has become more accurate through the use of vastly improved diagnostic procedures. These factors combined with advanced methods of anesthesia, hemostasis, replacement of blood volume, maintenance of electrolyte and fluid balance, and the use of antibiotics have reduced operative morbidity and mortality. A greater number of resectable tumors are being diagnosed and successfully removed with survival of useful patients.

Unfortunately, this has not been true in pediatric neurosurgery. Despite the same improvements in diagnostic procedures, operative techniques and clinical management, there has been no significant improvement in the results.

The diagnosis of neoplastic disease in the central nervous system of infants and children generally is not considered until the signs of increased intracranial pressure appear, and frequently not until this complication is well advanced. At this time the neurosurgeon may be completely thwarted in his attempts to localize the lesion or to remove it with any hope of recovering a neurologically functional person. Surgical management becomes an emergency, since the patient's life is in danger, often not primarily because of the tumor mass, but because of the increased pressure. Frequently the surgeon is confronted with an inoperable tumor and is forced to do only palliative surgery, such as decompression or shunting procedures.

The key to improved surgical management lies in earlier recognition, when surgical treatment has most to offer. Matson[11] has clearly indicated this in his report that 46 per cent of tumors of the central nervous system in the pediatric age group may be considered to be benign on the basis of their histologic type or anatomic location; at some time in their history these are surgically resectable and curable tumors.

INCIDENCE

Tumors of the central nervous system are the second most frequent neoplasms in infants and children, being exceeded in incidence only by leukemia. They occur only slightly less frequently in this age period than in adults, Greenwood and McGuire[5] having reported a ratio of about 1:1.4. Neoplastic disease may be present at any time from the first day of life, although reported cases during the first two years are few. There is an increase in incidence after the second year until the peak is reached in the 5- to 10-year age group. There is a decline in the frequency of intracranial tumors during the adolescent years.

DIAGNOSIS

The detection of disorders of the central nervous system secondary to neoplasms is infinitely more difficult in infants and children than in

adults. In adults we are dealing with an anatomically and physiologically fully developed central nervous system, the higher cortical centers of which mediate mentation and refined motor, sensory and discriminatory senses at a conscious level. Early disturbances of function are usually recognizable by the patient or his associates and will be expressed as a definable complaint. Patterns of motor and sensory deficit can be precisely mapped by careful neurologic examination. In addition, the fixed skull of the adult will allow only minimal intracranial expansion, and symptoms of increased intracranial pressure appear, therefore, early as an acute illness.

In infants and children, however, the central nervous system is a developing one which does not reach its highest level of function until early adolescent years. At birth, probably because of incomplete myelinization of nerve fibers, function is at a low phylogenetic level. All motor and sensory activity is of the most primitive type and is mediated through the spinal cord, brain stem and older portions of the midbrain. The remaining midbrain, the great mass of the cerebrum and much of the cerebellum are virtually nonfunctioning.

Function of the various conducting pathways is generally believed to coincide with their myelinization. The fibers of the pyramidal tract do not begin to receive their myelin sheaths until about the second month of life, and myelinization is not complete until about the second year. Association pathways in the higher cortical centers, which mediate fine discriminatory senses and mentation at the conscious level, do not begin to myelinate until much later and are not considered to be completed until the sixth to eighth year.

Detectable distortion of neurologic activity cannot be produced by lesions of the central nervous system until the tissue involved is physiologically functioning. Consequently, throughout much of the pediatric period, the child is incapable of subjectively recognizing altered neurologic function and cannot adequately describe the symptom. Accurate, detailed neurologic examination intended to define altered motor and sensory function often fails to do so simply because these neurologic changes are not present.

Associated with these difficulties in neurologic diagnosis is the fact that the ununited or infirmly united bones of the skull allow for increased intracranial expansion. The development of increased intracranial pressure is, therefore, often insidious and frequently is not detected until the tumor is greatly enlarged or until hydrocephalus is far advanced.

As a result of differences in the function and anatomy of the central nervous system and of the skull, the clinical manifestations associated with tumors of the central nervous system vary throughout the three pediatric age groups and will, therefore, be considered separately.

Infancy (Birth to Two Years)

Detectable disorders of neurologic function are the least prominent feature of tumors of the central nervous system in this age group unless the spinal cord or brain stem is involved. Neoplasms may grow to large proportions within the cerebrum and cerebellum, producing extensive damage to these structures, without creating objective neurologic signs. After the third or fourth month pyramidal tract involvement may be manifest by an increase in muscle tone of an extremity associated with fine tremor. Still later, gross weakness may be detectable. Alterations of fine discriminatory senses, such as apraxia, agnosia, defects of the visual fields, taste, smell, and so on, are not evident for obvious reasons. Convulsions secondary to neoplasms are rare in this age group and, when present, suggest involvement of the midbrain or basal ganglia.

Since the majority of tumors encountered in this period tend to grow in the midline or in the ventricle, they are in a position to block the cerebrospinal fluid pathways or alter the physiologic production of cerebrospinal fluid to the extent that hydrocephalus occurs quickly. Characteristically, the infant seems to be normal during the first few weeks or months of life. Normal development then seems to stop or, in many cases, actually regress. The child becomes restless and irritable, cries frequently and may feed poorly. Persistent vomiting is common and may lead to the preliminary diagnosis of milk allergy or some other feeding problem. There may also be unexplained fever without other signs of sepsis. Shortly thereafter, enlargement of the head becomes apparent and frequently will be clinically indistinguishable from congenital hydrocephalus. In tumors of the posterior fossa and third ventricle the enlargement of the head is symmetrical, but if the tumor involves only one hemisphere or one lateral ventricle, the greater enlargement is on the affected side (Fig. 3).

The differential diagnosis is usually that of hydrocephalus of nonneoplastic origin. In the latter, signs of hydrocephalus are detectable from birth or after an episode of meningitis or trauma. Actually, this clinical differentiation may be difficult. Final diagnosis is made by contrast air studies.

Childhood (2 to 10 Years)

At this age the sutures of the skull are closed and the bones are moderately firm. Actual fusion, however, does not occur until after puberty. Increased intracranial pressure is not usually accompanied by noticeable enlargement of the head, but is more likely to be manifest by headache, nausea, vomiting and papilledema. In the presence of slowly growing lesions these symptoms may be minimal, and the condition often is undetected for a long time.

Developmental improvement of function in the central nervous system is rapid during this age period, and cortical function is increased. Focal neurologic signs now begin to become detectable, but must be sought for with infinite patience, since the child is often incapable of volunteering or of describing a neurologic complaint, and his subjective response to neurologic testing is poor.

In this age group occurs the highest incidence of brain tumors in the pediatric period. Cerebellar astrocytomas, medulloblastomas, ependymomas and gliomas of the pons are the most common types. The clinical manifestations differ according to the location of the tumor.

INFRATENTORIAL. The most common site of intracranial tumors in the pediatric age group is in the infratentorial region. The neoplasms usually arise in the cerebellum or the wall of the fourth ventricle. Since this is a restricted area, obstruction of the fourth ventricle or aqueduct occurs early, and the predominant feature is obstructive hydrocephalus. The clinical manifestations are produced by this mechanism and are identical regardless of the type of tumor.

Early the predominant feature is a change in the child's disposition. This often leads to the diagnosis of an emotional disturbance and promotes long delay before neoplastic disease is suspected. The children characteristically become quiet, lose their initiative, have a tendency to cling to a parent and will often be restless and irritable and complain of headache.

The outstanding neurologic disturbance is alteration in the child's gait. Early he seems to be clumsy and will often lose his balance. Later it is noticed that he falls easily. This is a manifestation of truncal ataxia resulting from involvement of the vermis of the cerebellum. Often he prefers to remain indoors rather than play with other children. There is an associated hypotonia of both upper and lower extremities. Classic cerebellar signs, such as nystagmus, dysmetria, dyskinesia and gross disturbances of coordination, are not seen in midline tumors unless the hemisphere is involved.

Vomiting is a prominent feature and is due to direct involvement of the vagal nuclei in the brain stem. It appears early, is characteristically not associated with nausea and is commonly seen in the morning after breakfast. Curiously enough, the child will, after vomiting, eat another full breakfast and feel perfectly well.

As the tumor advances, there may be noted stiffness of the neck and tilting of the head to one side, usually to the side of the lesion, but sometimes in the opposite direction. Convulsive seizures are rare in subtentorial tumors unless there is associated involvement of the cerebrum.

SUPRATENTORIAL. Tumors of the cerebral hemispheres are more apt to produce focal neurologic signs than are infratentorial ones, especially

during the latter part of this age period. However, repeated neurologic examination may be necessary before the child's confidence is gained to such a degree as to permit accurate evaluation of any neurologic sign.

Alteration in motor function is the most frequent disturbance. Paresis may be initially suggested by an observation that the child seems to use one extremity less than the others. As the lesion progresses, actual motor weakness may be demonstrable. Changes in reflexes and the finding of pathologic reflexes, such as Babinski's sign and Hoffmann's sign, become more significant and are more indicative of involvement of the pyramidal tract. Sensory changes are more difficult to detect than are alterations in motor function.

Convulsions occur more frequently with supratentorial than with infratentorial tumors and may be valuable in localizing a suspected tumor, particularly if they are focal and are associated with postictal paralysis. An alteration in disposition is commonly observed and may manifest itself in many ways. Buchanan[3] has noted that children so affected seem to be particularly well behaved and more mature than is the average child of the same age. In contrast to subtentorial neoplasms, vomiting is an uncommon symptom until late in the course of the disease, whereas headache is a frequent initial complaint.

Preadolescent and Adolescent Age Groups (10 to 14 Years)

In this age group the diagnostic criteria of intracranial tumor are comparable to those in the adult. Functional development of the central nervous system has now almost reached its highest level. The child is capable of detecting alteration in his own neurologic function and may readily complain of deviations from the normal. Headache, focal neurologic deficits and convulsive seizures are commonly observed early in children with supratentorial tumors. In those with infratentorial neoplasms cerebellar dysfunction is readily detectable, and increased intracranial pressure is manifest early by headache, nausea, vomiting and papilledema.

In general, the clinical diagnosis of intracranial neoplasms throughout the pediatric period is fraught with many difficulties. The long delay in diagnosis is attributed to the frequency with which the symptoms are erroneously considered to be the result of disorders of the gastrointestinal tract, emotional disturbances, infectious diseases such as poliomyelitis or encephalitis, primary convulsive state, cerebral palsy, vascular accidents, degenerative diseases of the central nervous system and congenital hydrocephalus. These conditions occur more frequently than do neoplasms and are thus likely to be considered first in the differential diagnosis.

The constant feature of neoplastic disease is that it pursues a steadily progressive course. Individual symptoms, such as vomiting or headache, may seem to improve temporarily, but are usually replaced by another symptom, or the original manifestation returns in a more severe form. The over-all clinical picture is one of a relentlessly worsening condition. The physician must maintain a high degree of suspicion of tumor whenever signs and symptoms even remotely suggestive of a disorder of the central nervous system are present. This is especially true when the exact nature of the disorder cannot be established conclusively by laboratory means or when manifestations become progressively worse in spite of apparently adequate therapy. Under such circumstances specific diagnostic studies to establish the presence or absence of a neoplasm should be instituted promptly.

OPHTHALMOLOGIC EXAMINATION

Repeated examination of the eyegrounds is essential in all patients suspected of having disorders of the central nervous system. The development of papilledema is slow in infants and young children; enlargement of the head and other signs of increased intracranial pressure may be present before papilledema is evident. Nevertheless, although examination of the eyegrounds is difficult in this age period, its importance cannot be minimized.

In older children with closed suture lines, papilledema develops insidiously and may be present for a long period without other evidence of increased intracranial pressure. Consequently, repeated examination is essential. The first suggestion of its presence may be the discovery that the child cannot see the blackboard clearly in school. Frequently the presence of choked disks may be the only objective sign of intracranial disorder in a child with minimal signs and symptoms.

Examination of the visual fields is virtually impossible in the very young child and is not satisfactory until about the age of five or six years. Earlier, visual fields may be tested grossly by bringing attractive objects into the field of vision from behind and judging the ability of the child to visualize them by the motor response. A visual field defect is almost invariably of localizing value if its presence can be determined with any degree of reliability.

ELECTROENCEPHALOGRAPHY

The electroencephalogram is a valuable screening test which can be repeated frequently with no risk to the patient.

The presence of abnormal electrical activity, such as high amplitude, slow waves in one or more leads or diffuse slowing with maximal effect

on the occipital leads, is not specific enough to establish the presence of a neoplasm, nor are such findings sufficiently localizing to determine the surgical approach. Nevertheless abnormalities in the electroencephalogram may confirm the clinical impression of the suspicious physician and encourage him to proceed with contrast air studies or arteriography. On the other hand, a negative electroencephalogram does *not* rule out a brain tumor.

X-RAY EXAMINATION

X-ray examination of the skull is indispensable in evaluation of any disorder of the central nervous system and may be the first real indication of the presence of a neoplasm.

Fig. 1. Plain x-ray of the skull in an 8-year-old child. Anteroposterior projection demonstrates collection of calcium within the body of a tumor situated in the temporal lobe. Note splitting of the suture lines due to increased intracranial pressure.

Increased intracranial pressure is manifest by splitting or widening of the suture lines, particularly the coronal sutures. In advanced hydrocephalus the dorsum sellae may be eroded by the hydraulic pressure of the dilated third ventricle.

Accentuation of the convolutional markings of the inner table of the skull has generally been considered to be secondary to chronically increased intracranial pressure, but this fact is controversial. In the absence of other evidence of increased intracranial pressure, e.g., erosion of the dorsum sellae, its significance is doubtful.

Localized erosion or thinning of the inner table of the skull or of the

sphenoid ridge may indicate the presence of an adjacent tumor mass. This is often noted in the occipital bone in association with an astrocytoma.

Distortion of the sella turcica may be produced by an adjacent tumor mass, most frequently craniopharyngioma, in which case it is usually associated with suprasellar calcification.

Calcification rarely occurs in gliomas, but may occasionally be seen in ependymomas or mixed gliomas. It is usually distributed as fine flecks or an aggregate of calcium in the body of the tumor (Fig. 1). Calcification in the pineal gland is not a normal finding in children; when present, it is strongly suggestive of pineal tumor.

In the presence of any of these findings further x-ray investigation with contrast studies is mandatory.

Air Contrast Studies

Pneumoencephalography and ventriculography are the definitive studies for the detection and localization of intracranial tumors.

Pneumoencephalography, performed through the lumbar subarachnoid space, is the more precise study, but probably has not been adequately utilized for the detection of intracranial tumors in children. In most instances increased intracranial pressure is present at the time air study is considered, and, as a result, pneumoencephalography is associated with an increased risk to the patient. For this reason there is a widespread impression that the procedure is contraindicated at *any* time when neoplasm is suspected, especially one in the posterior cranial fossa.

On the contrary, pneumoencephalography performed by a *well-trained* operator using the positive pressure technique of air injection is a safe procedure which is well tolerated by infants and children, provided increased intracranial pressure is not present. Pneumoencephalography should be used for even minimal indications in any infant or child with an unexplained disorder of the central nervous system.

By necessity, *ventriculography* is the most frequently used procedure. In infants it can be performed by directing a needle through the coronal suture line into the ventricle opposite the side of the suspected tumor or into the potentially nondominant hemisphere. In older children bilateral trephine openings are made posteriorly, and a cannula is inserted into one or both ventricles. Cerebrospinal fluid is replaced volume for volume by air. The procedure not only permits visualization of the ventricular system, but also produces temporary decompression.

In the presence of tumor and increase of intracranial pressure, ventriculography may disturb the intracranial hydrodynamics to such an extent that a rapid increase in the already elevated intracranial pressure may be precipitated, further endangering the patient's life. Under such

circumstances ventriculography should be followed the same day by definitive surgery or a palliative decompressive procedure. When ventriculography is contemplated, the surgeon must be prepared to proceed immediately with a craniotomy.

Posterior fossa tumors are usually diagnosed by inference only, since ventriculography often demonstrates only symmetrically dilated lateral and third ventricles; because of mechanical blockage of the fourth ventricle, the posterior fossa may not be visualized. In such instances, with a cannula in the ventricle, ventriculography can be supplemented by films taken after injection of air into the lumbar subarachnoid space, using the positive pressure method with the patient in the upright position; by this means the posterior fossa may be visualized and the tumor more clearly defined (Fig. 2).

In the presence of advanced ventricular enlargement, total drainage of the ventricles and replacement of the fluid by air are not advisable because of the high degree of risk to the patient. In such instances a so-called bubble study may be used. Fifty to 60 cc. of fluid are exchanged for air in one ventricle. By properly manipulating the head, the bubble is maneuvered into all portions of the ventricular system, and x-ray films are taken in each position. This study must be performed with great care, however, and every portion of the ventricular system must be visualized. With large ventricles and only a small amount of air, a tumor of the cerebrum can be easily overlooked. It must be kept in mind that the hydrocephalus which thins out the cerebral hemisphere will also "iron out" a soft glioma in the hemisphere to nearly the same contours and make visualization extremely difficult.

CEREBRAL ANGIOGRAPHY

In the past 10 years cerebral angiography has become a valuable addition to the surgeon's diagnostic armament. Unlike ventriculography, in the presence of increased intracranial pressure it will not disturb intracranial hydrodynamics and precipitate a chain of events requiring emergency surgery. The films can be studied leisurely when dry, and surgical approach carefully planned. When a neoplastic lesion is depicted, it can usually be identified as such, and a clue to the histology may be provided. More important, the vascular supply to the tumor is visualized, which is of inestimable value in planning the surgical approach. This is the only study which will demonstrate vascular anomalies, such as aneurysms and angiomas.

TUMOR TYPES

In adults approximately 45 per cent of intracranial tumors are gliomas and involve predominantly the cerebral hemispheres. In children, how-

ever, 80 per cent are gliomas. They tend to grow in the midline of the neural axis and are thus apt to involve the vermis of the cerebellum, the fourth ventricle and brain stem. Consequently the majority of intracranial neoplasms in children are subtentorial. When they are located in the supratentorial region, they tend to be in the vicinity of the ventricles.

The most frequently appearing cell types are the ependymoma, astrocytoma and medulloblastoma, which make up the 80 per cent of all tumors in this age group. The most common nongliomatous tumor is the craniopharyngioma. The remaining types, each of which accounts for only a small percentage of all intracranial neoplasms in infants and children, are the papillomas of the choroid plexus, hemangiomas, pinealomas, teratomas, metastatic tumors and an occasional meningioma. Pituitary adenomas and acoustic neuromas do not occur in children. Tuberculomas, which at one time were the most common intracranial "tumor" in childhood, are now virtually nonexistent in this country.

The clinical signs and symptoms of an intracranial tumor are produced wholly by its effect upon the nervous tissue involved and are, therefore, identical regardless of the cell type, except for the time element; the latter, of course, varies with the rate of growth. There are, however, certain characteristics of each tumor type which are worthy of mention.

Ependymomas

In our experience this has been the most frequent type of intracranial neoplasm, accounting for 24 per cent of all such tumors. This percentage is much higher than in other reported series of intracranial tumors in children. The degree of malignancy varies considerably, ranging from highly malignant neoplasms to others which are at least histologically benign. They tend to grow wherever ependymal cells are located and may thus appear anywhere in relation to the ventricular system and spinal cord. In our experience there has been no preponderance above or below the tentorium. In many instances these tumors are relatively slowly growing, and their onset is often insidious. This is the type of glioma most likely to calcify, and it may, therefore, be evident on the plain x-ray film of the skull.

It is generally felt that at some time in its evolution this neoplasm is histologically benign; if it is favorably situated anatomically, it is thus a resectable and curable tumor. Unfortunately, by the time the neurosurgeon encounters these neoplasms, their invasive nature often precludes total removal, and the recurrence rate is high. Cerebral ependymomas often reach enormous size before being detected and either

invade or arise from the basal ganglia and paraphysial area, making total excision impossible. Those in the posterior fossa are usually intimately associated with the fourth ventricle and medulla, thus obviating removal.

Astrocytoma

The cerebellar astrocytomas are histologically benign tumors which are often cystic. They occur with the same frequency as do medulloblastomas in children in the 4- to 10-year age group. They are not highly invasive, and, because of their tendency to grow slowly, the clinical manifestations are often insidious. Vomiting, headache and disturbances in gait and personality are outstanding features. Localized cerebellar signs and nystagmus may be detected when the tumor involves one hemisphere.

In spite of the dramatic size of some of these tumors, they are usually completely resectable, and the surgical results are excellent for long survival with minimal neurologic deficit. However, if they are resected only after prolonged delay in diagnosis and after increased intracranial pressure has produced extensive irreversible damage to the cerebrum, survival will be associated with permanent neurologic sequelae.

Astrocytomas involving the cerebral hemispheres are much less common. Because of their tendency to invade the basal ganglia and midbrain as solid tumors, they are often not as amenable to surgical excision.

Medulloblastoma

This is probably the most highly malignant of all intracranial neoplasms. It usually arises in the roof of the fourth ventricle. It occurs throughout the pediatric period, but is most common between the fourth and tenth years of life. The tumor grows rapidly, invades the fourth ventricle and frequently implants itself in the subarachnoid space and spinal canal.

Because of its rapid growth in the midline of the posterior fossa, the clinical manifestations are usually of shorter duration than those of astrocytoma and are predominantly the signs of internal hydrocephalus. Vomiting is common, as are generalized hypotonia and truncal ataxia.

Surgical removal of these tumors is impossible. Management consists in removal of enough tumor to re-establish the circulation of the cerebrospinal fluid and in performing palliative decompressive procedures. The tumor is highly radiosensitive, and x-ray therapy should be given postoperatively to the posterior fossa and entire spinal canal. Recurrence of the tumor may thus be delayed. Invariably, however, there is a fatal termination.

Glioma of the Brain Stem

The prognosis of medulloblastoma is practically hopeless because of its malignant cell type. Gliomas of the brain stem have a similar prognosis, not because of their malignancy, but because of their anatomic location. They are usually histologically benign, but grow in the substance of the pons and medulla and are neither surgically resectable nor amenable to radiation therapy. Contrary to the usual clinical picture of intracranial neoplasms in infants and children, this tumor produces objective neurologic signs of dysfunction of the cranial nerves, pyramidal tract and sensory deficit early, regardless of the age of the patient. Characteristic-

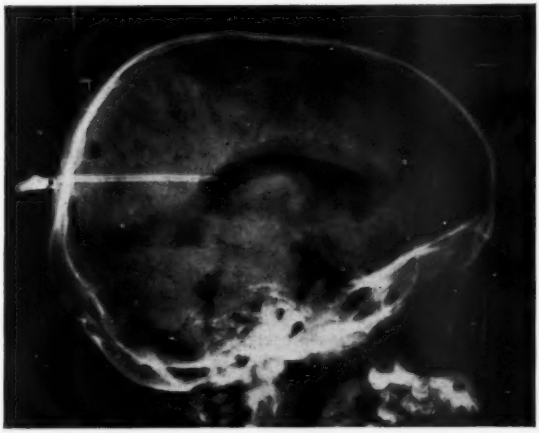

Fig. 2. Glioma of the pons. Air contrast study in 6-year-old child with sixth and seventh cranial nerve palsy and right-sided paresis. Ventriculography performed because of associated congenital anomaly of the craniovertebral junction and possible internal hydrocephalus. Ventriculography supplemented by injecting air into lumbar subarachnoid space. Note large size of the pons. Tumor proved by autopsy.

ally, increased intracranial pressure does not develop until late in the course of the disease.

The diagnosis is made by contrast air study. If definite enlargement of the pons is demonstrated, surgical intervention is not indicated. The average time of survival is less than a year (Fig. 2).

Craniopharyngioma

This tumor, derived from embryonal cell rests in the suprasellar region, is the most frequent nongliomatous tumor in children. Because of its position, several types of clinical manifestations may be observed.

Pituitary dysfunction is common and is manifest by retarded growth, decreased metabolism, sexual infantilism and poor response to stress. As

the tumor expands, encroachment upon the adjacent hypothalamus may be responsible for diabetes insipidus, hypothalamic seizures, hypothermia or hyperthermia or disturbances in the normal sleep pattern. Eventually there is encroachment on the optic chiasm and optic tracts, usually with resultant bitemporal hemianopsia. As the tumor enlarges, usually as a multiloculated cyst, increased intracranial pressure may be produced.

The diagnosis is usually made on the plain x-ray film in which distortion of the sella and suprasellar calcification are apparent. Occasionally air studies are necessary to confirm the diagnosis.

Total surgical excision is hazardous because of the location of the tumor and its proximity to the pituitary and, more important, to the hypothalamus. Postoperative pituitary and hypothalamic crises have been significantly reduced by the preoperative and postoperative use of ACTH. Total removal is rarely accomplished, but partial removal or decompression of a cyst will reduce pressure on the adjacent vital structures and may alleviate symptoms for a long time.

Tumors of the Choroid Plexus

These are rare neoplasms, but are important because of the distinct clinical picture they present and because they occur almost exclusively in infants.

The *papilloma* usually appears in the glomus of the choroid plexus of

Fig. 3. Infant, age 18 months. Clinical manifestations of progressive hydrocephalus. Ventriculogram demonstrates enormous enlargement of one lateral ventricle with a large tumor within the ventricle. Proved by surgery to be papillary carcinoma of the choroid plexus. Note asymmetrical ventricular enlargement.

the lateral ventricle, but may occasionally occur in the third or fourth ventricle. It produces increased amounts of cerebrospinal fluid, and the clinical picture usually mimics that of communicating hydrocephalus. Ventricular tap yields darkly xanthochromic fluid with excessively high protein. The tumor can be clearly identified on the ventriculogram, and total surgical excision can be accomplished successfully. Occasionally, however, these may be invasive, malignant neoplasms. Their removal is then often followed by rapid recurrence (Fig. 3).

The remaining types of tumors, such as hemangioblastoma, pinealoma, mixed gliomas, unclassified tumors and teratoma, are infrequent. Their manifestations depend upon the location of the lesion and the age of the child. Resectability varies with the cell type and the anatomic location of the neoplasm.

SUMMARY

Intracranial neoplasms are the second most frequent type of neoplasm encountered in infants and children, being exceeded only by leukemia. They may occur at any time during the pediatric age period, but the peak incidence is between 5 and 10 years of age.

The clinical manifestations are the result of local destruction of nervous tissue by the neoplasm and by increased intracranial pressure. Since the neural pathways are immature in infants and children, neurologic localization of neoplasms is difficult. Moreover, increased intracranial pressure may be present for some time before being recognized because the incompletely united sutures of the skull permit expansion of the cranial contents. Unfortunately, therefore, the diagnosis of intracranial tumor is commonly not suspected until the tumor is well advanced and has produced extensive, often irreversible, damage to the central nervous system. At this time surgical management has little to offer. For this reason it is generally felt that intracranial neoplasms in infants and children carry a uniformly poor prognosis. Unquestionably the medulloblastomas and gliomas of the pons are virtually hopeless lesions, but a large percentage of the astrocytomas, ependymomas, craniopharyngiomas and other types are at some time resectable and therefore curable tumors if they can be discovered and removed before they have produced irreversible neurologic damage.

The physician must maintain a high level of tumor-consciousness toward any patient with signs and symptoms of disorder of the central nervous system who demonstrates a steadily progressive, worsening condition in spite of apparently adequate treatment. *Repeated* neurologic examination and inspection of the eyegrounds are mandatory. Electroencephalography and plain x-ray studies of the skull may demonstrate pertinent findings. Air contrast studies and cerebral angiography are the

precise studies for tumor diagnosis. Only by repeated, careful clinical evaluation and unhesitating use of the proper diagnostic studies in patients with even minimal unexplained signs suggesting disorder of the central nervous system will the diagnosis be established earlier than is now commonly the case, and will significant reductions in the morbidity and mortality of these tumors be accomplished.

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3701 N. Broad St.
Philadelphia 40, Pa.

RETINOBLASTOMA

JOHN S. MC GAVIC, M.D.

Retinoblastoma is the most common intraocular tumor in childhood; other primary tumors of the retina are extremely rare. About 100 such tumors are diagnosed in the United States each year. Although the diagnosis is made in children at an average age of one and one half to two years, these tumors are really congenital in origin. Retinoblastoma has also been reported in premature infants. About one third are bilateral. There is no predilection for race or sex. Retinoblastomas have been reported sporadically and also in several generations of a family. A person who has survived a retinoblastoma is likely to have children with bilateral retinoblastomas, so that it is important to advise such people not to have children. On the other hand, unaffected parents of one child with retinoblastoma need not fear that further offspring will have them, the chances being the same as in the general population.

The following *clinical signs* suggest the possibility of retinoblastoma: (1) a grayish-yellow reflex from behind the pupil, (2) strabismus, (3) one dilated pupil, (4) phthisical eyes when the cause is unknown. There are frequently multiple sites of origin within the same retina in addition to bilateral occurrences in over one third of the cases.

The *diagnosis* is made by examination with an ophthalmoscope. Both pupils should be fully dilated, and general anesthesia may be necessary. *Both eyes should be examined.* In 75 per cent of the cases calcium deposits can be demonstrated by x-ray examination. Radioactive phosphorus (P^{32}) is no help in diagnosis, despite the fact that these are rapidly growing, highly cellular tumors. Transillumination is of little value.

DIFFERENTIAL DIAGNOSIS

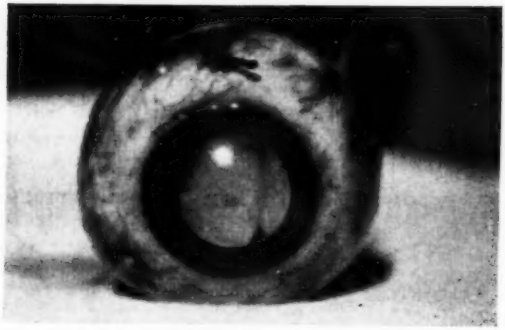
Tunica vasculosa lentis is a congenital anomaly occurring in one or both (usually one) eyes of usually full term infants. The eye is smaller

than normal, shows a gray membrane presenting its concave surface just behind the lens, and has long ciliary processes which extend in well central to the equator of the lens so that they are readily visible. The pupil dilates with difficulty. Other congenital anomalies are sometimes present, including those in the angle of the anterior chamber.

Metastatic retinitis following blood stream infections in children results in an umbrella-shaped complete detachment of the retina. There may be no inflammatory signs in the anterior segment of the eye.

Retinopathy of prematurity (retrolental fibroplasia) occurs almost exclusively in premature infants who have been given oxygen as a supportive measure. It may be unilateral or bilateral. In severe cases difficulty may be encountered in differentiating this condition from retinoblastoma. Retrolental fibroplasia shows the major changes in the periphery of the retina and anterior vitreous. Separation of the retina is a common sequel of contraction of the new blood vessels which sprout from the retina into the vitreous. Secondary glaucoma is not uncommon. The history may be deceptive, since retinoblastoma can occur in premature infants as well as those born at term. Examination

A



B

Fig. 4. (*Legend on page 361.*)

C

Fig. 4. Clinical appearance of retinoblastoma. A, Retinoblastoma of the right eye showing the reflection of light through the pupil to the tumor surface. B, An enucleated eye, which contains a retinoblastoma, showing the tumor as seen through the pupil. C, The appearance of a retinoblastoma as seen with the ophthalmoscope. Newly formed blood vessels and some white punctate foci of calcium are present. (Reese: *Tumors of The Eye*. Paul B. Hoeber, Inc.)

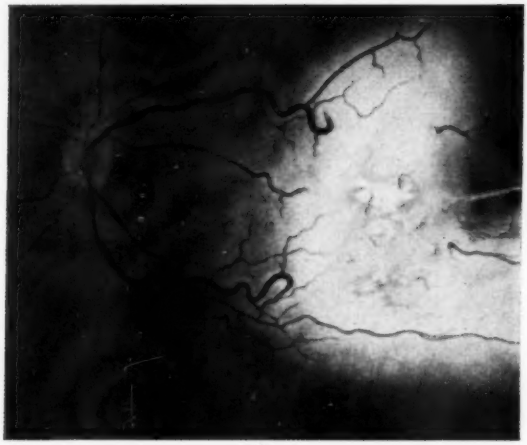
with the ophthalmoscope, under general anesthesia if necessary, will usually suffice to differentiate these two conditions. In at least one case bilateral retinoblastoma was mistaken for retrolental fibroplasia.

Since the eye is often useless in cases in which differentiation is difficult, enucleation for diagnosis is sometimes advisable.

Massive retinal fibrosis follows hemorrhage into the retina at birth. It produces a diffuse grayish-white mass extending out from the fundus without producing detachment of the retina. The condition is rare.

Toxoplasmosis is usually a congenital infection transmitted from an apparently well mother to the fetus. The ocular lesions are usually central and may give a fundus reflex suggestive of retinoblastoma. Although there are calcium deposits in the brain in toxoplasmosis, none is present in the eyes. This is in contrast with retinoblastoma, which shows intraocular calcium deposition in three out of four cases, but has no deposits in cerebral tissue.

Medullated nerve fibers may be present over the nerve head or in the retina away from the nerve head. They are flat, yellow and brush-shaped, with frayed borders. Careful examination will readily differentiate this variation-of-normal from retinoblastoma.



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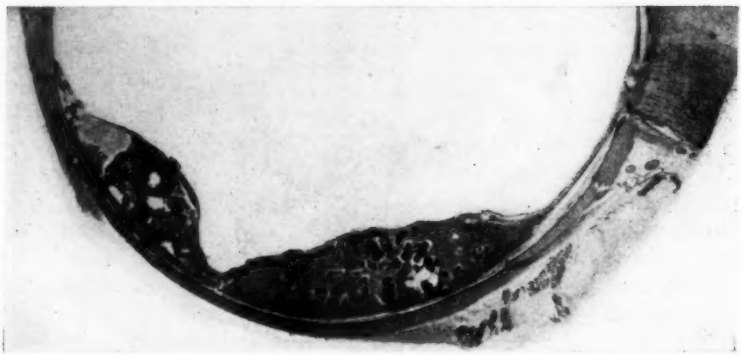

B

Fig. 5. Calcium deposition as seen clinically and microscopically. A, The fundus lesion with the rather sharply demarcated chalky white areas of calcium in the central portion. B, Microscopic section of the same eye showing the sharply demarcated black foci of calcium occurring in areas where the tumor is necrotic. (Reese: *Tumors of the Eye*. Paul B. Hoeber, Inc.)

Coat's disease is a group of poorly defined massive exudative and hemorrhagic involvements of the retina. An opaque elevation of the retina is seen, often associated with aneurysmal dilatations of the retinal vessels.

Drusen of the optic nerve head and retina occur alone or with other evidences of tuberous sclerosis. They are pearly-gray and have a distinctly nodular appearance. They may be confused with retinoblastoma

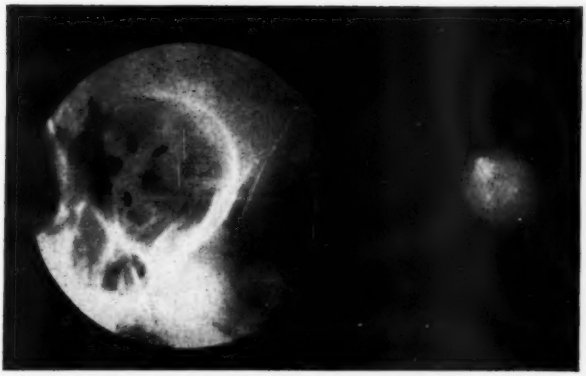

Fig. 6. Detection of calcium in the tumor by roentgenogram. A girl, aged 3, was brought for examination because of a whitish pupil of the left eye which had been observed for 6 months. Stereoroentgenograms of the left orbit revealed a fairly large shadow of calcium in the position of the eye. The eye was enucleated, and the roentgenographic examination again showed the large mass of calcium. The pathologic diagnosis was retinoblastoma. On the left is a roentgenogram before operation, and on the right is one of the eye after enucleation. (Reese: *Tumors of The Eye*. Paul B. Hoeber, Inc.)

containing calcium. Again careful ophthalmoscopic examination is sufficient to differentiate this condition from retinoblastoma.

HISTOPATHOLOGY

The histopathology of retinoblastoma can be closely correlated with the clinical findings. Knowledge gained in the laboratory can be applied to patients better than in many diseases.

These tumors are congenital. Frequently there are multiple primary sites of origin within the same retina. In at least one third of the affected infants the tumor is bilateral. Furthermore, seeding of the tumor to other sites of the same eye is a characteristic finding. These implantations grow readily.

The tumors can be divided into those with rosettes (called neuroepitheliomas) and those without rosettes; the latter are considered less differentiated. They arise from the nuclear layers of the retina, usually the inner layer. The tumor cells resemble the cells of the nuclear layers. Mitotic figures are numerous. Cellular growth is greater around blood vessels, with characteristic necrosis of cells further from their source of nutrition. This manner of growth and degeneration gives rise to cylindrical pseudorosettes. Calcium becomes deposited in the necrotic areas.

True rosettes are small spherical growths of cells arranged around

a space lined by a cell membrane. These are the only evidence of differentiation shown by retinoblastomas. A pseudorosette may contain hundreds of true rosettes.

Spread into the optic nerve often extends only to the lamina cribrosa. In 27 per cent it extends beyond this site, but in only 9 per cent does it extend as far back as the operative section.

Spread into the choroid occurs in 25 per cent of the cases. From here generalized metastases occur. Spread through the sclera is seen in 10 per cent of the globes studied histologically.

TREATMENT

When retinoblastoma is unilateral, the safest treatment is enucleation of the involved eye. The other eye should be re-examined at repeated intervals because over one third of the children have bilateral involvement, and the second eye may have a much smaller tumor which may have been missed on previous examinations.

When both eyes are involved, the safest treatment is still bilateral enucleation. Because parents often refuse permission for removal of both eyes, other means have been sought. Usually one eye has a more extensive tumor, and this eye is enucleated. X-ray therapy for the other eye has been used for many years, with fair success, but accompanied by serious complications, including cataract, intractable secondary glaucoma and rhabdomyosarcoma in the adjacent muscles due to irradiation. Retinoblastoma can be cured by x-ray, but large doses are required. Many eyes had later to be removed because of complications, especially the intractable secondary glaucoma.

In the past few years triethylene melamine (TEM) has been combined with x-ray. The results have been excellent, the latest report claiming 90 per cent cures. TEM is given by intra-arterial injection. It alone does not cure these tumors, but lesser doses of x-radiation are necessary to effect cures when the two are combined.

It should be noted that extensive multiple tumors and those with tumor cells loose in the vitreous do not respond to this combined treatment.

The bulk of the bilateral retinoblastomas in the United States are treated at the Institute of Ophthalmology in New York City, where a team of experts with the best equipment is available. The figures are those furnished by this group.

PROGNOSIS

Until 1955 about 50 per cent of the children with retinoblastoma died. This figure included all retinoblastomas, unilateral and bilateral, and whether or not x-radiation was used.

Bilateral cases have become more frequent since there are more survivors to further the hereditary factor. If no treatment is given, the mortality is 100 per cent. Taken as they come, treatment by enucleation results in 50 per cent mortality. Treatment with x-ray plus TEM is said to have reduced the mortality to only 10 per cent in bilateral cases.

The methods of spread of this tumor are twofold—one is direct extension via the optic nerve to the brain. This is a natural progression, since the optic nerve is made up of axons of the ganglion cells of the retina.

The second method is extension into the highly vascular choroid, which allows fatal generalized metastasis by blood stream. No treatment is of any avail in either of these situations.

If the tumor becomes seeded in the orbit by (1) aspiration biopsy through the sclera or (2) by direct extension through the sclera or (3) by failure to excise all the involved optic nerve at enucleation, radon seeds or x-radiation therapy can be used. No accurate figure on the results can be given, but the prognosis is guarded.

Since early diagnosis permits more adequate treatment, the inescapable conclusion is that all infants should have careful examination of their eyes as a routine measure. Those with strabismus or abnormal reflexes behind the pupil should be most carefully examined. Prompt and robust treatment is necessary to save the lives of children with retinoblastoma.

601 Montgomery Avenue
Bryn Mawr, Pa.

TUMORS OF THE HEAD AND NECK

JAMES B. AREY, M.D.

Tumors of the head and neck comprise a heterogeneous group of neoplasms of epithelial and mesenchymal origin, as well as tumors derived from totipotential cells (teratomas). Many of the neoplasms are not peculiar to this region, but are also observed in other sites, e.g., teratomas, rhabdomyosarcomas and osteosarcomas. No attempt will be made to discuss all the neoplasms which may be observed in the head and neck. Instead, only those tumors will be discussed which are largely peculiar to this area or which, although also observed elsewhere, present particular clinical problems because of their location.

For *lymphoma* and *hygroma colli*, see pages 633 and 530.

TUMORS OF THE MAJOR SALIVARY GLANDS

Chronic parotitis may simulate a neoplasm from which it may be differentiated only by biopsy. However, a history of repeated episodes of swelling of the gland, often bilateral, should suggest the possibility of an inflammatory rather than a neoplastic process. Biopsy of the mass rather than excision in toto is preferable in such instances, since it is much less apt to be followed by paralysis of the facial nerve.[12]

Mixed tumors of the major salivary glands are predominantly neoplasms of adults, but may also be observed in infants and children. They arise most frequently in the parotid gland and present as a round firm mass just beneath the lobule of the ear. The mass is usually painless, but may be associated with some form of local discomfort;[8] in some instances pain may be referred to the ear. Histologically, the neoplasms consist of a variety of admixtures of epithelial and mesenchymal-like elements. The tumor is apt to recur, and once recurrent it is even more likely to produce later recurrences. Metastases, however, are uncommon.

From St. Christopher's Hospital for Children and the Departments of Pediatrics and Pathology, Temple University School of Medicine, Philadelphia.

Mucoepidermoid carcinomas probably arise from the ducts of the salivary glands. They contain mucus-secreting cells, epidermoid and nonmucus-secreting cells. These tumors usually arise in the parotid gland and are interpreted clinically as mixed tumors; they are, however, less common than mixed tumors. The initial complaint is commonly that of painless swelling; especially in the more malignant lesions, however, pain may be present and may even antedate the appearance of the mass. In general, the prognosis is graver than is that of patients with mixed tumors. A significant number of the neoplasms not only recur locally, but also metastasize to the regional lymph nodes and to bone, lung, brain or subcutaneous tissue.

Adenoid cystic carcinomas (cylindromas) are probably even more infrequent in children than are mucoepidermoid carcinomas. They are adenocarcinomas with a rather distinctive histologic pattern consisting of anastomosing cords of small, dark epithelial cells between which are rounded acellular areas which may contain mucus; tumors of similar histologic appearance arise from the mucus-secreting glands of the mouth, pharynx, paranasal sinuses, trachea or bronchi. Clinically, the manifestations are similar to those of mixed tumors, but pain and even paralysis of the facial nerve are somewhat more frequent because of the invasive nature of these neoplasms. They are best treated by surgical excision, the response to irradiation usually being unsatisfactory. The tumor is apt to recur locally. Metastases to regional lymph nodes or even to distant sites may take place, but usually not until one or more local recurrences have occurred.

Papillary cystadenoma lymphomatosum (Warthin tumor) is a rare benign tumor arising in the parotid gland or its vicinity. It is composed of papillary epithelial elements intimately admixed with well developed lymphoid tissue in which germinal centers are common. These tumors occur predominantly in males. Their histogenesis is debated, but they may arise from inclusions of salivary gland within lymph nodes located either in the body of the parotid gland or adjacent to this; such inclusions, which may be entirely ductal, are commonly observed in and about the parotid gland in routine studies of this organ. The usual clinical diagnosis in a patient with a papillary cystadenoma lymphomatosum is that of a mixed tumor, but it may also be confused with a branchial cyst, cervical lymphadenitis or a malignant lymphoma involving the cervical lymph nodes. The tumors are benign, but may recur.

Hemangioma of the parotid gland is often associated with a hemangioma of the overlying skin. Preauricular swelling is commonly noted at the time of birth, and the mass frequently grows rapidly during the first several months of life. In spite of the cellularity of these tumors, they are clinically benign, and there is evidence to indi-

cate that they undergo differentiation and become more quiescent after four to six months of age.[29] The tumors may respond to irradiation, but surgical removal is probably the treatment of choice at present. However, particular care must be taken to avoid the facial nerve, which is more superficially located in the infant than in the adult. It seems possible that spontaneous regression of these tumors might take place just as occurs with cutaneous hemangiomas, but definite proof of this is not available to date.

Lipomas and *fibrosarcomas* may arise in the parotid gland in children, but are extremely rare.[12]

TUMORS OF THE NASAL CAVITY, ACCESSORY NASAL SINUSES, PHARYNX, EAR AND ORAL CAVITY

Nasal gliomas are rare congenital anomalies consisting of masses of glial tissue and occasionally neurons.[16] They usually manifest themselves as a subepidermal tumor located over the bridge of the nose and present since birth.[7] Sometimes, however, they may occur as intranasal polypoid masses, and even less frequently both intranasal and extranasal masses may be present. The extranasal type presents as a smooth, round, fixed or movable mass over the bridge of the nose; it may extend to the inner canthus of one eye. Clinically, these masses have been mistaken for hemangiomas.[9, 19] The extranasal and the intranasal gliomas should be differentiated from encephaloceles, since removal of the latter may be complicated by the development of meningitis. Differentiation is usually possible on the basis of detailed roentgenographic or anatomic studies, since most nasal gliomas have no anatomic connection with the brain; in a few instances, however, defects of the underlying bone which are sealed with fibrous tissue have been noted in association with nasal gliomas. These are not true neoplasms[6] and probably arise from cells which have been separated from the anterior part of the brain during embryonic life.

Nasal polyps are not true neoplasms, but are chronic inflammatory lesions characterized by the presence of pedunculated masses of edematous mucosa arising from the turbinates or from the accessory sinuses; many of them probably arise upon an allergic basis. The manifestations are those of chronic nasal obstruction and discharge, sometimes associated with headache. The diagnosis is established by direct visualization, the polyps appearing as single or multiple white, relatively avascular, edematous masses.

Papillomas are rare benign tumors arising from the epithelium of the nasal mucosa or of the paranasal sinuses. Single or multiple irregular polypoid masses may be present. Recurrences are common, sometimes occurring at a different site from the original tumor.[23]

Adenomas are benign tumors arising from the glands of the mucous membrane of the nasal or paranasal cavities. They manifest themselves by nasal obstruction and sometimes by swelling in the region of the nose or cheek. Epistaxis is common. The tumors located in the ethmoidal region may erode the adjoining bone. Local recurrence is common, and the prognosis is guarded because of the difficulty of complete removal of these slowly growing, expansile tumors.[23]

Tumors of the minor salivary glands may arise in the mucous membrane of the nose, paranasal sinuses, pharynx or mouth, especially the palate. Since they arise from glands similar to those of the major salivary glands, the histologic types of neoplasms are comparable to those observed in the latter sites, i.e., mixed tumors, mucoepidermoid carcinomas and adenoid cystic carcinomas (pp. 549, 368); at least in adults, however, tumors arising in the minor salivary glands are somewhat more frequently mucoepidermoid carcinomas than are those arising in the major glands.[3] Tumors of the minor salivary glands may occur at any age. They most commonly arise from the posterolateral aspect of the hard palate, where they encroach upon the inner surface of the alveolar process adjoining the molar teeth. Palatal tumors commonly project into the floor of the nasal cavity and maxillary sinus as well as into the oral cavity. Thus these tumors, as well as those arising in the nasal cavity or in the paranasal sinuses, may be responsible for mechanical obstruction of the nasal passageway. Tumors arising in the ethmoid may be responsible for swelling in the region of the base of the nose, exophthalmos and obstruction to the lacrimal ducts. Bleeding may occur as a result of ulceration of the tumor. Metastases are infrequent, but recurrences are common. Surgical removal is the treatment of choice, but some of the tumors, especially those in which epithelial elements predominate, may respond to irradiation.

Carcinomas of the mucosa of the nasal cavity, paranasal sinuses, pharynx or mouth are rare in early life.[20] They are usually highly undifferentiated neoplasms, referred to as transitional cell carcinomas or lymphoepitheliomas, which may be histologically indistinguishable from lymphosarcomas (p. 633). The primary neoplasm, which is most frequently located in the nasopharynx, is a diffusely infiltrative growth which may metastasize to the cervical lymph nodes before it is responsible for local manifestations. The tumors are highly radiosensitive, but their prognosis is grave.

Olfactory neuroepithelial tumors are rare malignant neoplasms arising from neuroepithelial elements in the nasal fossa. The presenting complaint is usually that of unilateral nasal obstruction, sometimes associated with recurrent epistaxis. Unilateral exophthalmos or swelling at the root of the nose may be observed when the neoplasm has extended beyond the confines of the nares. Initially the lesion may be

observed high on the medial or lateral wall of the nasal fossa, but when first seen one side of the nasal fossa is usually partially or completely filled with a polypoid mass of tumor tissues; in some instances a history of recurrent "nasal polyps" has been obtained.[18] The tumors consist of sheets of undifferentiated cells which may form pseudorosettes or true rosettes. Areas of necrosis are commonly present, and there may be foci of calcification within the neoplasm; histologically, the appearance may resemble that of a neuroblastoma, a retinoblastoma or even a lymphoma; the tumors are highly malignant and may invade the paranasal sinuses, hard palate, intraorbital tissues or bones of the skull and may metastasize to the bones and lungs as well as to the cervical lymph nodes. They are very radiosensitive and are probably best treated by a combination of surgical excision and irradiation. Although the prognosis is grave, a number of cures have been obtained.

Rhabdomyosarcomas arising in the head and neck in infants and children are predominantly embryonal in nature, the more classic, better differentiated forms of rhabdomyosarcoma being less frequent in the early age groups.[11] Although arising most frequently in the orbit, they may also arise from the facial, cervical or palatine muscles as well as from the nasopharynx, mastoid, middle ear, sinuses or tonsil; embryonal rhabdomyosarcomas arising just beneath the mucous membrane and projecting into a cavity frequently assume a polypoid or grapelike configuration and have been referred to as *sarcoma botryoides*.[11, 22] The presenting complaint is usually that of a mass, but other manifestations may also be noted, depending upon the site of the tumor, e.g., strabismus, dysphagia or aural discharge; pain is present when a nerve is involved by the tumor. Slight fever and leukocytosis may be observed, usually as a result of ulceration and secondary infection. The neoplasm is a highly malignant one which spreads locally and may metastasize to the regional lymph nodes and viscera. There is a great tendency of the tumor to local recurrence, and early wide excision is the treatment of choice. Radiation therapy is a valuable adjunct to surgery.[27] The mortality rate is high, but cures have followed early radical treatment.

Juvenile nasopharyngeal angiofibromas are relatively rare neoplasms arising in the nasopharynx. They occur almost exclusively in males, usually in the teen-age group.[26] The most frequent manifestations are those of nasal obstruction and epistaxis. Nasal obstruction results from occlusion of one or both posterior nasal orifices, and the mass often protrudes into the nasal cavity itself. Palatal or facial deformities, exophthalmos or visual disturbances may occur with continued growth and expansion of the neoplasm, and roentgenograms sometimes reveal invasion of the occipital or sphenoid bones. Epistaxis occurs as a result of rupture of one or more of the numerous vessels which are an integral part of the neoplasm. Metastases do not occur, but because of their location, vascu-

larity and invasive tendency complete removal may be impossible. Surgical removal, irradiation or a combination of these may be used in treatment; severe hemorrhage is common during surgical removal, but may also occur postoperatively or after radiation therapy. The effect of androgenic therapy is not completely evaluated, but it has been used as an adjunct to more definitive treatment. Rarely the neoplasm may regress spontaneously with sexual maturity.

Chemodectomas (nonchromaffin paragangliomas) are rare tumors arising in the chemoreceptor system, e.g., the glomus jugulare, the carotid body, the ganglion nodosum of the vagus nerve or the aortic bodies; tumors arising from more than one of these sites may be observed in a single patient.[17, 30] The tumors occur almost entirely in adult life, although a chemodectoma of the glomus jugulare has been observed in a child.[4] Tumors arising in the glomus jugulare are responsible for nonspecific clinical manifestations, often of long duration. These include the presence of an aural polyp which tends to bleed profusely after slight trauma and to recur after removal, progressive loss of hearing, chronic otorrhea and facial paralysis.[14] The tumor is characteristically a soft, dark red or purplish polypoid mass which appears to arise in the middle ear and often extends into the external auditory meatus. It may destroy the adjoining bone by expansion or, in the rare malignant type, by actual invasion. Only rarely do metastases occur to the regional lymph nodes or viscera, but because of gradual extension into adjoining structures these tumors should be treated by radical surgical removal.

Eosinophilic granuloma (p. 568) may occur in almost any bone, but is most commonly observed in one of the bones of the skull; more than one bone may be involved, either at the same time or after an interval of varying periods of time. In the mastoid process the lesion may be associated with clinical manifestations similar to those of inflammatory disease of the mastoid. Roentgenographically, the lesion is a sharply defined round or oval radiolucent defect without sclerosis of the surrounding bone. Curettage will usually suffice to cure the local lesion, which also responds to irradiation. Lesions of identical appearance roentgenographically and histologically may be observed in Hand-Schüller-Christian disease and in Letterer-Siwe disease; the differential diagnosis is dependent upon the demonstration of extraosseous lesions in the latter two diseases, the age of the patient and the clinical course of the disease, but transitions between these three diseases are occasionally observed. As a rule, however, the prognosis of eosinophilic granuloma of bone is excellent.

Chordomas are rare tumors derived from remnants of the notochord. They usually arise in the sacrococcygeal region or base of the skull,

where they invade and destroy the adjoining bone. The initial manifestations of a chordoma of the base of the skull may be the result of projection of the neoplasm into the nasopharynx or may be those of an intracranial tumor. Owing to their location, operative removal is impossible. Some chordomas in children have apparently responded to irradiation.

Teratomas (p. 573) in the head and neck in infants are usually well differentiated tumors, but their location often precludes complete surgical removal. They may arise from the base of the skull, in the roof of the pharynx or in the palate and project into the cranial cavity, nose or mouth; in some instances both intracranial and extracranial tumors may be present, being connected by an isthmus passing through the sphenoid. Well differentiated teratomas extending out of the mouth have been designated as epignathi. Because of their size and location these tumors are usually fatal at or shortly after birth. Teratomas may also arise from the region of the thyroid and present as a large cervical mass in a newborn infant.[21]

Lymphangioma (p. 529) may be responsible for a localized tumor of the tongue or for diffuse macroglossia. The lesion may be present at birth or may not be apparent for months or even years. Intermittent glossitis is a common complication. Localized tumors are best treated surgically; some of the diffuse forms will respond to irradiation.

Hemangioma (p. 511) of the tongue is a less frequent cause of macroglossia than is lymphangioma. It is usually deep red and tends to bleed more easily than does the lymphangioma.

Neurofibroma of the tongue is a rare lesion which may be responsible for unilateral macroglossia. It usually develops before the age of three years and is often associated with other evidences of neurofibromatosis. In contrast to macroglossia caused by angiomatous lesions, the neurofibroma is usually noncompressible and relatively avascular. Excision of the tumor may necessitate a major surgical procedure, since there is a tendency for the mass to extend to the floor of the mouth and throughout the neck.[1]

Myoblastoma is a small, superficial, spherical benign tumor composed of large granular cells. It is most frequently observed in the tongue, especially on the dorsum. The cell of origin is not established unequivocally. A benign tumor of similar histologic appearance may be observed in the gingiva at the time of birth;[2] it occurs predominantly in females on the incisor area of the maxillary gingiva and has been referred to as a *"congenital epulis."*

The *lingual thyroid* is a mass of thyroid tissue at the base of the tongue in the region of the foramen caecum. In some instances, in which there has been complete failure of descent of the thyroid, it may

be the only existing thyroid tissue; removal in such instances is, of course, followed by hypothyroidism.

TUMORS OF THE LARYNX

Papillomas are the most common neoplasms of the larynx in children. They are usually multiple and may arise from any site in the larynx or even from the trachea or bronchi. The initial manifestation is that of persistent hoarseness which may be associated with a dry cough. With growth of the tumors attacks of dyspnea occur; rarely death from suffocation has been reported in association with these lesions. Direct laryngoscopy reveals multiple, superficial, pink verrucous or filiform lesions. They should be treated by superficial excision with forceps through the laryngoscope, care being taken not to injure the normal tissues. Although repeated recurrences are common, these lesions in children are not premalignant and, at least in some instances, may regress at puberty. Radical surgical procedures are, therefore, contraindicated.

Hemangiomas (p. 511) of the larynx in infants are rare. They are usually subglottic in location and in over half of the patients other hemangiomas are present, usually on the head and neck.[10] The clinical manifestations are dyspnea and stridor, usually apparent during the first three months of life; hemoptysis is infrequent.[13] Irradiation is probably the treatment of choice, but this is often followed by increase in the size of the mass, and in most instances a tracheotomy must be performed. The reported mortality rate is high.

TUMORS OF DENTAL ORIGIN

The classification of tumors of dental origin is extremely elaborate and complex, and some of the lesions have been differentiated on the basis of such minor histologic variations that their inclusion as distinct entities hardly appears justified. They are usually benign tumors, many of which are probably more correctly regarded as malformations rather than true neoplasms. Only a few of the lesions which have been reported will be discussed here.

Ameloblastomas are true neoplasms derived from epithelium having the potentiality of forming an enamel organ. Although occurring predominantly in adult life, they have also been observed in infants and children. The tumor arises most frequently in the mandible as a painless lesion which may be detected only by roentgenographic examination. With continued growth, however, deformity of the jaw and face and rarely pain may ensue. Tumors arising in the maxilla may obliterate the antrum and bulge into the orbit, nasal cavity or mouth. Roentgenographically, the lesion presents as a multilocular or unilocular

discrete radiolucent area; small, round, accessory radiolucent areas may be observed in the adjoining bone as a result of extension of the neoplasm, and the roots of the teeth upon which the tumor is encroaching are resorbed.[25] Ultimately the neoplasm may expand and destroy the cortex and invade the adjoining soft tissues. The tumor is radioresistant and is best treated by some form of surgical resection. Although recurrences are common after simple curettage, metastases are rare.

Rare pigmented tumors which characteristically arise in the maxilla or less frequently in the mandible of infants have been referred to as *melanotic ameloblastomas;* since the origin of these tumors is disputed, they have also been called *retinal anlage tumors* and *melanotic progonomas.*[5, 28] They are invasive neoplasms which destroy the bone in which they arise. They should, however, be treated by conservative surgical procedures, since recurrences are infrequent, and to date metastases from these tumors have not been reported.

Odontomas, strictly defined, are tumors of odontogenic origin. In general, however, they are considered to be tumors in which both the epithelial and mesenchymal elements of the teeth have differentiated to varying degrees.

Soft odontomas are probably true neoplasms. They occur most commonly in the mandible, where they grow slowly and enlarge by expansion rather than infiltration of the bone. The tumor is often discovered accidentally during roentgenographic examination, although in some instances there may be slight swelling of the jaw or pain. Roentgenographically, the appearance may be indistinguishable from that of an ameloblastoma. The tumor consists of undifferentiated connective tissue containing islands of epithelial cells, and thus contains odontogenic elements of both ectodermal and mesodermal origin. It should be treated by conservative surgical means since there is little tendency to recurrence. Differentiation of these lesions from fibromas arising as a result of proliferation of only the mesenchymal elements of the tooth germ may be difficult or impossible, since inclusions of small amounts of epithelium may be observed in these exclusively mesenchymal tumors (*odontogenic fibromas*).

Hard odontomas are probably malformations rather than true neoplasms. They are usually asymptomatic lesions which appear roentgenographically as an irregular mass of calcified material surrounded by a narrow radiolucent band with a smooth periphery. Histologically, they consist of various admixtures of enamel, dentin and cementum, sometimes simulating small teeth. They should be treated by surgical removal. When sheets and cords of epithelial cells are present in addition to the better-differentiated structures, the lesion has been referred to as an *ameloblastic odontoma;* these commonly recur and, therefore, necessitate more extensive surgical removal.[24]

TUMORS OF SKIN APPENDAGE ORIGIN

Although tumors of skin appendage origin are by no means confined to the skin of the face or scalp, certain of them occur predominantly in this area and are, therefore, included in this section. In general, they tend to behave in a clinically benign manner, and the neoplastic nature of all of them is not accepted. Only a few will be described.

Syringocystadenoma papilliferans usually appears as a single verrucous plaque, most frequently on the scalp. The surface of the plaque may be crusted, and multiple minute cysts are sometimes visible within the isolated lesion. Histologically, numerous papillary processes project into the lumens of dilated ducts; the latter are continuous with the surface of the overlying skin and with glandular structures located in the deeper dermis.

Trichoepithelioma (epithelioma adenoides cysticum) is a tumor derived from hair follicles. It is frequently familial, usually appearing in girls at the time of puberty as multiple small yellow to pink nodules on the skin of the face and occasionally on the upper trunk. Histologically, the overlying epidermis is intact, but beneath it are multiple cysts of varying size lined by stratified squamous epithelium; nests of basal cells proliferate from the walls of these cysts and may simulate the appearance of a basal cell carcinoma.

Cylindromas (turban tumors) are often familial. They occur predominantly on the scalp of females, sometimes appearing in early childhood or at puberty. They are usually observed first on the forehead as smooth, firm, freely movable painless nodules. The tumors increase in number and in size throughout life, so that ultimately the entire scalp may be covered by a lobulated mass of tumors. They are nearly always benign and are best treated by surgical excision.

Adenoma Sebaceum

Numerous small yellowish brown nodules are often observed in the malar region of children with tuberous sclerosis. These are not true neoplasms, but are hamartomas composed of various admixtures of sebaceous glands, hair follicles and hyperplastic capillaries; in some instances there is no apparent increase of sebaceous glands.[15] These cutaneous manifestations of tuberous sclerosis are not usually apparent in infancy.

TUMORS OF THE SKIN

Epidermoid cysts are not true neoplasms. They may arise from congenital ectodermal rests or from inclusions of epidermis resulting from trauma. They are spherical, benign tumors which are often located in the skin of the scalp, face or neck.

Dermoid cysts cannot be differentiated clinically from epidermoid cysts. They are often located in the skin of the forehead, especially in the supraorbital region. Histologically, they are cystic spherical masses lined by stratified squamous epithelium and containing skin appendages in their walls. Dermoid cysts also occur in the calvarium, where they are demonstrable roentgenographically as sharply demarcated defects surrounded by sclerotic bone.

Calcifying epitheliomas may be confused clinically with epidermoid cysts. Some authors attribute them to epithelial proliferation and secondary degeneration within an epidermoid cyst. They may occur at any site, but are especially apt to involve the face or upper extremities, where they appear as hard, sharply demarcated tumors. They are benign, but may be erroneously interpreted as carcinoma because of the proliferation of epithelial cells within them.

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2600 N. Lawrence St.
Philadelphia 33, Pa.

DIFFERENTIAL DIAGNOSIS OF MEDIASTINAL MASSES

JOHN W. HOPE, M.D.

C. EVERETT KOOP, M.D.

The mediastinum is a space in the median portion of the thorax separating the pleural sacs of the two lungs. It extends from the sternum ventrally, to the vertebral column dorsally, and comprises all the thoracic viscera except the lungs and pleurae. Most textbooks divide the mediastinum arbitrarily into an upper and a lower part by a line running from the sternal angle ventrally to the fourth intervertebral disk dorsally. The upper portion is then spoken of as the superior mediastinum. The lower portion is in turn subdivided into three parts: the anterior mediastinum, in front of the pericardium; the middle mediastinum, containing the pericardium; and the posterior mediastinum, behind the pericardium.

In the posteroanterior chest roentgenogram all the mediastinal contents and masses appear to be in the same plane, and it is impossible to determine where they actually lie. It is only in the lateral view that one can decide whether a structure is anterior, posterior or medial. Most of the mass lesions involving the mediastinum can be diagnosed with a high degree of accuracy simply by knowing whether they occur in the front, in the middle or in the back. Few of these lesions respect the arbitrary division set by anatomists between the upper and the lower mediastinum, with the result that one often has to say that a certain tumor occurs in the superior and anterior mediastinum or in the superior and posterior mediastinum. For the purpose of reaching a roentgen diagnosis of a mediastinal mass lesion, therefore, it seems more logical to

From the Department of Radiology and the Surgical Clinic, The Children's Hospital of Philadelphia, and the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine, Philadelphia.

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divide the mediastinum into only three compartments: an anterior, a middle, and a posterior, and to carry these three all the way cephalad to the superior aperture of the thorax.

Such an arbitrary division is seen in Figure 7, where the space has been divided into almost equal thirds. The anterior mediastinum is that portion lying in front of a line drawn down to the diaphragm from the

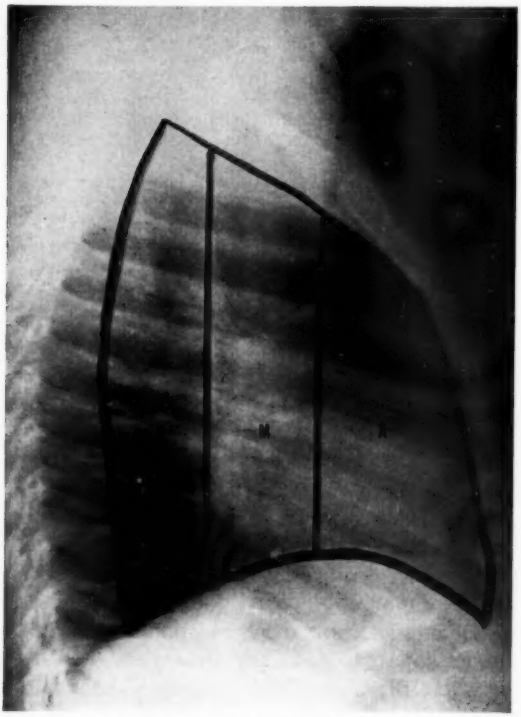


Fig. 7. Lateral chest roentgenogram showing the divisions of the mediastinum used in this article: *A*, anterior mediastinum; *M*, middle mediastinum; *P*, posterior mediastinum.

upper edge of the manubrium. The posterior mediastinum is that portion lying behind a line drawn down to the diaphragm from just dorsal to the trachea. The middle mediastinum consists of the interposed tissues between the anterior and the posterior portions. Such a departure from the usual anatomic description may seem presumptuous, but we are discussing differential diagnosis from the roentgen standpoint, and most of the mass lesions commonly encountered in infants and children will clearly fall into one of these three compartments.

ANATOMIC CONTENT OF THE THREE DIVISIONS OF THE MEDIASTINUM

In using the foregoing arbitrary division of the mediastinum to arrive at a differential diagnosis of a mass lesion, it is necessary to know the principal contents of each compartment.

The *anterior mediastinum* contains the thymus, the anterior mediastinal lymph nodes, the substernal extension of the thyroid if one is present, and the anterior portion of the pericardium and heart. It should also be remembered that a congenital defect in the anterior segment of the diaphragm called the foramen of Morgagni is in the most anterior, inferior portion of the anterior mediastinum.

The *middle mediastinum* contains the posterior portion of the pericardium and heart, the aortic arch, the origin of the great vessels to the upper extremities and to the head and neck, pulmonary arteries, superior and inferior vena cava, the trachea, the main bronchi entering the lung roots, the lymph nodes in relation to the trachea and bronchi, and the phrenic nerves.

The *posterior mediastinum* contains the esophagus, the thoracic duct, the descending thoracic aorta, the vagus and splanchnic nerves, and the azygos and hemiazygos veins. Actually, the paravertebral sympathetic nerve trunks and intercostal nerves do not lie within the mediastinum, but tumors arising from these nerve tissues grow forward into the posterior mediastinum. Therefore, for practical clinical purposes, this nerve tissue is regarded as being within the posterior mediastinum.

LOCATION OF MASS LESIONS IN THE MEDIASTINUM

By knowing the anatomic contents of each arbitrary division of the mediastinum, lesions can now be grouped with a high degree of accuracy. Such a grouping is given below, not necessarily in order of frequency.

ANTERIOR MEDIASTINUM	MIDDLE MEDIASTINUM	POSTERIOR MEDIASTINUM
Thymic enlargements	Lymphomas	Neurogenic tumors
Thymomas	Lymph node inflammations (tuberculosis, sarcoid and acute exanthemas)	Duplications of the foregut (gastroenteric cysts)
Teratomas	Aneurysms	Neurenteric cysts
Lymphomas (anterior mediastinal lymph nodes)	Congenital anomalies of the great vessels	Bronchogenic cysts
Lymphangiomas		Lesions of the esophagus
Pericardial cysts		Diaphragmatic hernias (foramina of Bochdalek)
Intrathoracic goiters		Mediastinal meningoceles
Diaphragmatic hernias (foramen of Morgagni)		

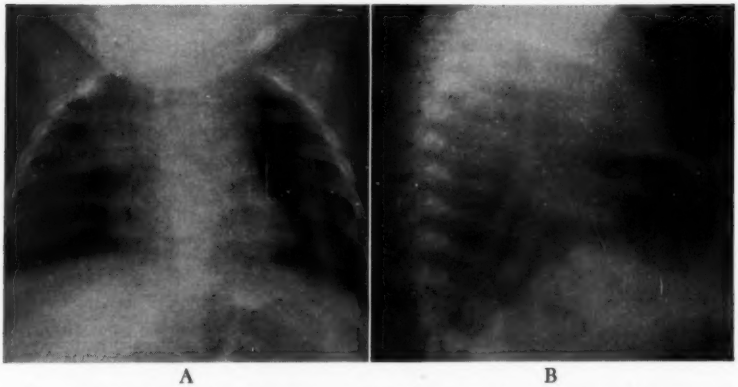
ANTERIOR MEDIASTINAL LESIONS

Thymic Enlargements

Of all the mediastinal mass lesions, the so-called thymic hyperplasias are the most common. This would naturally be the case, since the thy-

mus is a normal structure and is present in the mediastinum at all ages. There is a wide range of normal variations in the size and shape of the thymus. During infancy and early childhood the thymus is relatively larger, compared to the size of the anterior mediastinum, than later on in life, and for this reason widening of the upper mediastinum is expected in the posteroanterior roentgenogram of the chest.

The most characteristic thymic roentgen shadow is the one shown in Figure 8. Here the tail of the thymus projects out from the right hilus,

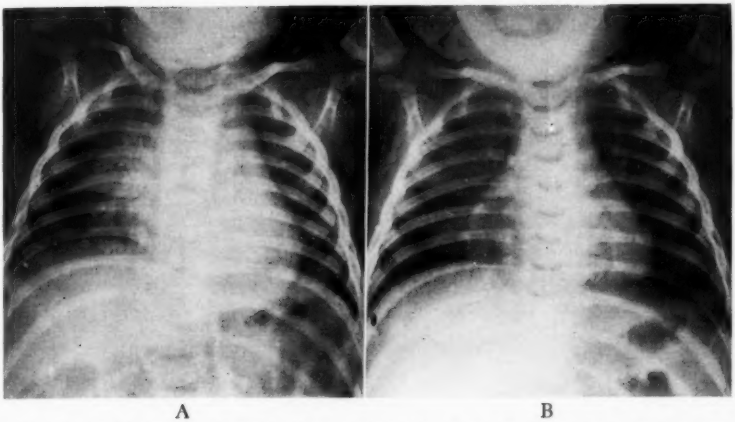


A B

Fig. 8. A 5-month-old male infant examined because of an upper respiratory tract infection. A, Anteroposterior chest roentgenogram showing a typical thymic "sail" shadow extending out from the right superior mediastinum (arrow); B, lateral chest roentgenogram with the thymus filling the anterior superior mediastinum (arrow). There is no tracheal compression.

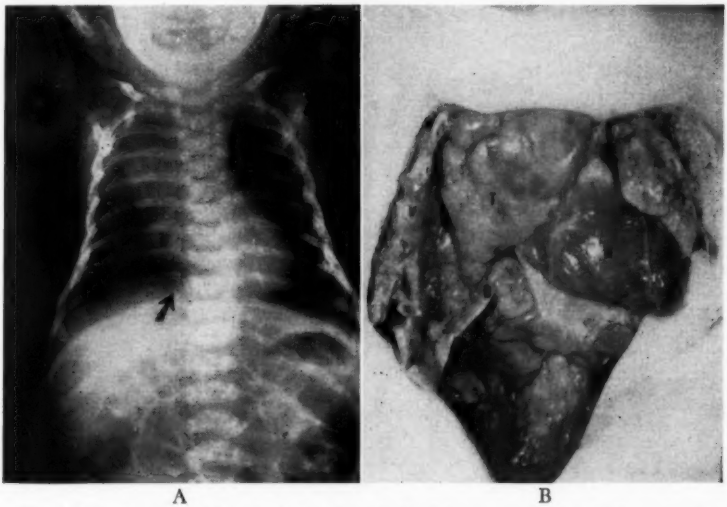
producing a "sail" shadow. The phase of respiration greatly alters the size of the thymic silhouette. In Figure 9 the thymic density is prominent during expiration, but in inspiration almost disappears into the mediastinum. Slight degrees of obliquity often greatly exaggerate the apparent size of the thymus. The thymus does not always produce the characteristic roentgen appearance seen in Figure 8; often its tail extends to the diaphragm (Fig. 10), or its entire shadow may be on the left (Fig. 11), or it may produce a bilateral widening of the mediastinum.

It is our opinion that roentgen diagnosis of a significant pathologic enlargement of the thymus should not be made. At The Children's Hospital of Philadelphia up to the present time there has never been a case of tracheal obstruction due to an enlarged thymus gland. The trachea of normal infants is retrodisplaced, buckles, and partially collapses during expiration. It is this normal expiratory phenomenon observable to a greater or less degree in every normal baby which in the past caused much concern about the significance of an apparently en-



A B

Fig. 9. An 18-month-old male infant examined because of an upper respiratory tract infection. *A*, Anteroposterior chest roentgenogram in partial expiration with the right hemidiaphragm at the level of the eighth rib posteriorly. There appears to be a moderately large thymus gland. *B*, Anteroposterior chest roentgenogram during a more inspiratory phase of respiration with the right hemidiaphragm at the level of the ninth rib posteriorly. Most of the thymus gland is no longer visible. The 2 radiographs were made within 30 seconds of each other. (This case was previously shown in *Medical Radiography and Photography*.)



A B

Fig. 10. A 2-month-old male infant hospitalized because of amyotonia congenita. *A*, Anteroposterior chest roentgenogram showing a mediastinal mass on the right side, extending all the way down to the diaphragm (arrow). *B*, Photograph of the post-mortem examination 4 days after the chest roentgenogram: *T*, thymus gland; *H*, heart; *D*, diaphragm. The thymus gland corresponds to the mediastinal shadow seen in the roentgenogram.

Fig. 11. Posteroanterior chest roentgenogram of a 15-month-old female infant in whom a superior mediastinal mass had first been detected at 12 months of age. In spite of 3 x-ray treatments (50 roentgens [air] each) delivered to the anterior superior mediastinum, the mass persisted (arrow). The mass was excised and proved to be a normal thymus gland.

larged thymus. In our opinion one is never justified in radiating the thymus gland to prevent tracheal obstruction. If the trachea is truly obstructed during inspiration, this condition derives from some lesion other than the thymus gland.

Thymomas

Tumors of the thymus gland are mentioned at this time, not because of their frequency, but because it is logical to follow a discussion of the normal thymus with a discussion of the abnormal thymus. To date, at The Children's Hospital and at St. Christopher's Hospital for Children in Philadelphia,* the pathologic diagnosis of a thymoma has not been made. This apparently is a tumor of the anterior mediastinum rarely encountered in adults, and almost never in infants and children.

Teratomas

The second most common mass lesion found in the anterior mediastinum of infants and children is the teratoma. Since another clinic of this symposium is devoted entirely to a discussion of teratomas (p. 573),

* Personal communication with Dr. James Arey, Pathologist, St. Christopher's Hospital for Children.

it is not the purpose here to give a pathologic description. The time-honored term "dermoid cyst," originally used to describe a benign tumor of displaced tissue made up only of ectodermal derivatives, is usually a misnomer, since careful search of multiple sections will reveal derivatives of other germ layers. The terms "benign teratoma" (dermoid cyst) and "malignant teratoma" are preferable.

These tumors lie in the anterior mediastinum and are often asymmetrical, with enlargement to the left more frequent than to the right. Often dense calcific areas are seen within the mass (Fig. 12). When

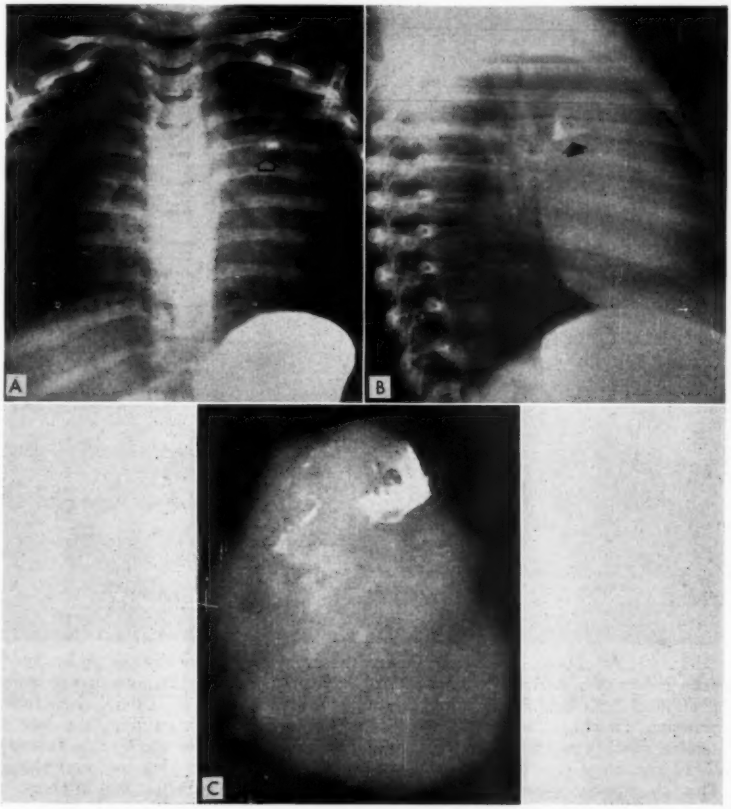


Fig. 12. A 14-month-old male infant who at the age of 5 months was found to have an anterior mediastinal mass lesion. This was treated by x-ray before admission to The Children's Hospital of Philadelphia. *A*, Posteroanterior chest roentgenogram showing the mass lesion on the left with an irregular calcific density (arrow). *B*, Lateral chest roentgenogram showing the mass to lie in the anterior mediastinum. The calcification has a triangular shape (arrow). *C*, Roentgenogram of the resected tumor, which proved to be a benign teratoma.

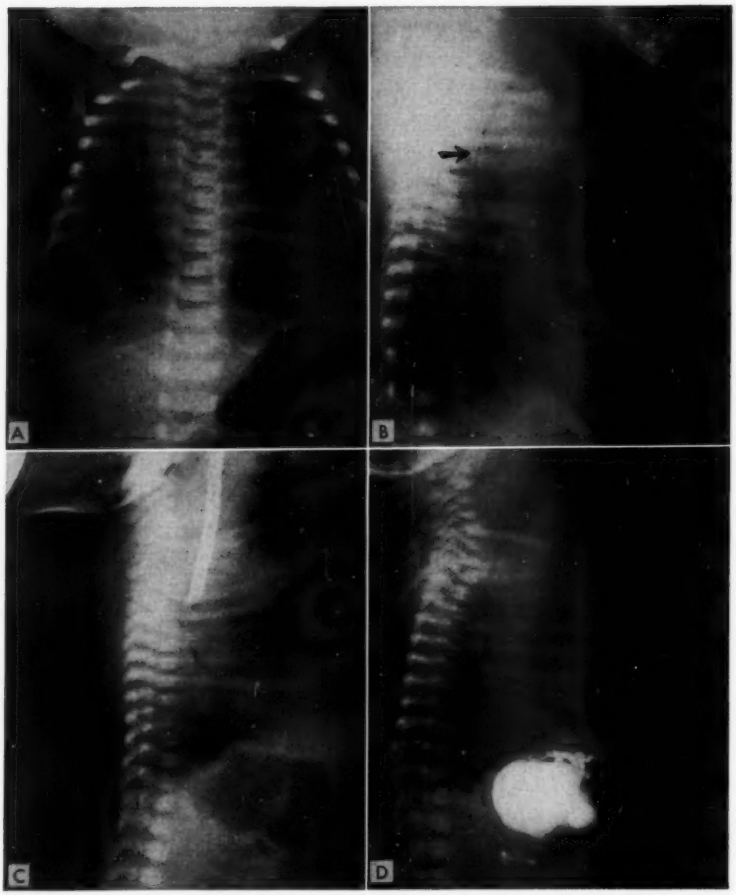


Fig. 13. An 11-day-old male infant with severe respiratory distress and cyanosis since 2 days of age. *A*, Anteroposterior chest roentgenogram showing extreme hyperaeration of both lung fields and a wide superior mediastinum. *B*, Lateral chest roentgenogram showing extreme hyperaeration of the lungs and a mass filling the anterior mediastinum, producing posterior deviation and compression of the trachea (arrow). *C*, Lateral chest roentgenogram taken after the introduction of a laryngeal airway. The tube was too short to relieve the obstruction, and the baby was still in great distress. *D*, Lateral chest roentgenogram taken after a polyethylene tube had been passed to the carina. As soon as this tube was passed the baby began to breathe freely for the first time. The tumor was excised and proved to be a benign teratoma lying behind a normal thymus gland and in front of the trachea.

calcium is present in the tumor, it is easy to differentiate a teratoma from a thymus, but there are times when it is difficult to differentiate the two. Since the thymus gland almost never compresses the trachea during inspiration, an anterior mediastinal mass lesion producing tracheal compression is most probably a teratoma (Fig. 13). Few mediastinal teratomas are malignant when encountered during infancy and childhood.

Lymphomas

Because of the predominance of lymph nodes in relation to the trachea and bronchi, lymphomas are most common in the middle mediastinum. There are, however, some lymph nodes in the anterior mediastinum, so that occasionally a lymphoma will present primarily at this site. The appearance of these tumors is variable, but usually there is a scalloped periphery with vague borders. Figure 14 is a good example of a *lymphosarcoma* which, from the lateral view, is seen to lie chiefly in the anterior mediastinum.

Lymphangiomas

Cavernous lymphangiomas (*cystic hygromas*) are common lesions in the cervical region of infants and children. Occasionally the mass may extend through the thoracic inlet into the mediastinum; when this occurs, it is the anterior mediastinum which is most often involved. It is rare for one of these lesions to present as an isolated tumor in the mediastinum. These lesions usually pose no differential problem because the mass in the neck is obvious and the direct extension is visible on the roentgenogram. The thoracic mass tends to increase in size during inspiration and to decrease during expiration; the converse is true of the cervical mass. They may also have lateral extensions into the adjacent axilla.

Pericardial Cysts

These cysts are usually adherent to the parietal pericardium and present in the right cardiophrenic angle anteriorly. With oblique views there is evidence of demarcation of the lesion from the cardiac shadow. This differentiates a pericardial cyst from a fat pad. These cysts are extremely rare in infants and children, and none has been found at The Children's Hospital of Philadelphia. Of the 27 cases on file at the Armed Forces Institute of Pathology, only one occurred in a six-year-old

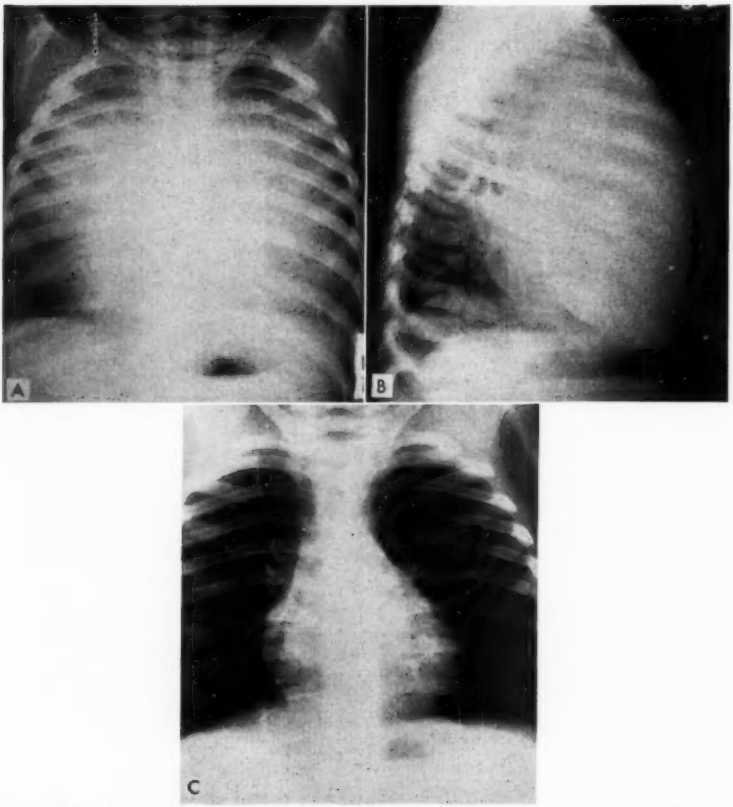


Fig. 14. A 2-year-old male infant admitted to hospital because of respiratory distress of 3 weeks' duration. The cervical lymph nodes were enlarged and firm. Biopsy proved a diagnosis of lymphosarcoma. *A*, Posteroanterior chest roentgenogram showing a huge central mass merging with the heart and completely obliterating the cardiac contour. The periphery of the mass blends off into a vague border. *B*, Lateral chest roentgenogram showing the mass completely filling the anterior mediastinum and encroaching upon the middle mediastinum. There is some fluid at the bases posteriorly. *C*, The child was treated with 600 roentgens (tissue) to the mediastinum, and the mass entirely disappeared. In this posteroanterior chest roentgenogram, taken 6 months after the radiation therapy, the mediastinum still appears normal. At this time, however, the peripheral blood showed a typical picture of lymphatic leukemia, and the boy died 3 months later.

child; the rest were in adults. Figure 15, a good example of a pericardial cyst, occurred in a 19-year-old youth; so the case actually falls well above the age group being described. It is included to show the typical location and appearance should such a lesion be encountered in a younger child.

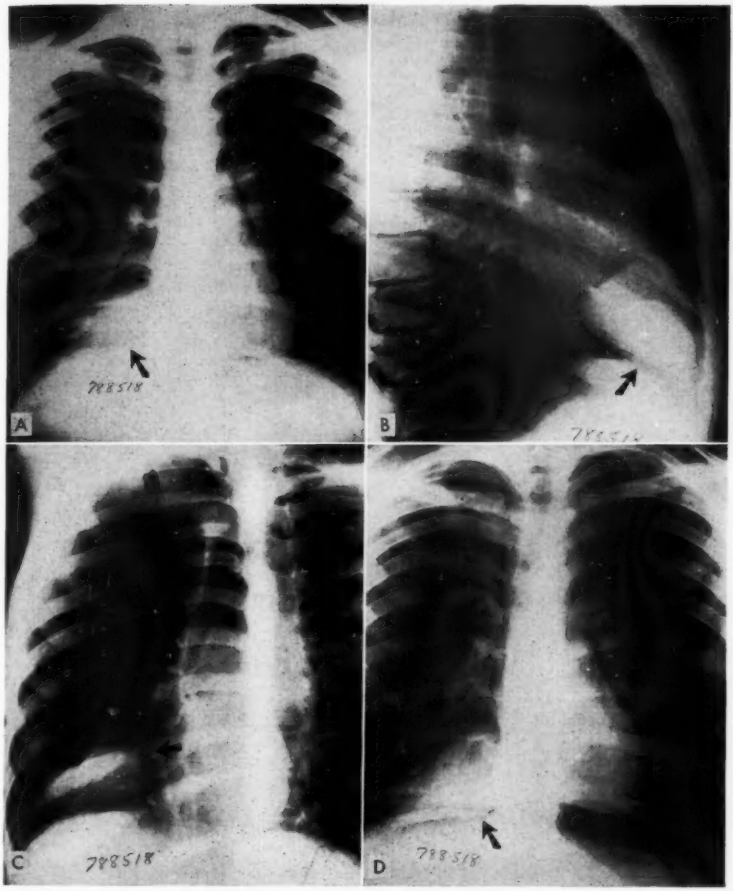


Fig. 15. A 19-year-old youth in whom an anterior mediastinal mass was discovered as an incidental finding in the course of a routine chest x-ray. The mass was excised and proved to be a pericardial cyst. *A*, Posteroanterior chest roentgenogram showing a mass in the right cardiophrenic angle (arrow); *B*, lateral chest roentgenogram showing the mass lying anteriorly (arrow); *C*, left anterior oblique view showing a line of demarcation between the cyst and the heart border (arrow); *D*, posteroanterior chest roentgenogram following a pneumoperitoneum, showing the mass lying above the diaphragm (arrow). (Courtesy of Armed Forces Institute of Pathology—Accession Number 788518.)

Intrathoracic Goiters

Considering the frequency of substernal thyroids in the adult, it is interesting that no intrathoracic goiter has been surgically removed at either The Children's Hospital or St. Christopher's Hospital for Chil-

dren in Philadelphia.* On rare occasions, during a postmortem examination on a child, a small substernal thyroid appears as an incidental finding, but in our experience none of these has ever given rise to symptoms or was recognized during life.

Diaphragmatic Hernias

The most common lesion in the anterior-inferior mediastinum of infants and children is a diaphragmatic hernia through the foramen of

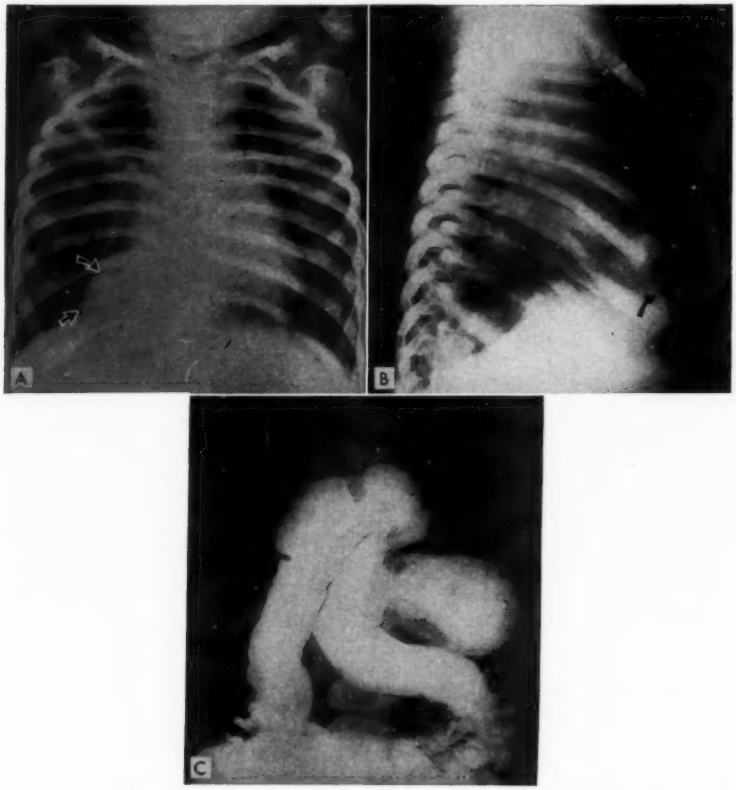


Fig. 16. A 20-month-old male infant admitted to hospital because of recurrent abdominal pain. *A*, Posteroanterior chest roentgenogram showing a mass in the right cardiophrenic angle (arrows) similar to the pericardial cyst seen in Figure 15, *A*. *B*, Lateral chest roentgenogram showing a loop of bowel lying anterior to the heart (arrow). *C*, Anteroposterior roentgenogram of a barium enema, with barium also in the stomach, showing a loop of transverse colon above the diaphragm in the midline. This is a diaphragmatic hernia through the foramen of Morgagni.

* Personal communication with Dr. James Arey, Pathologist, Saint Christopher's Hospital for Children.

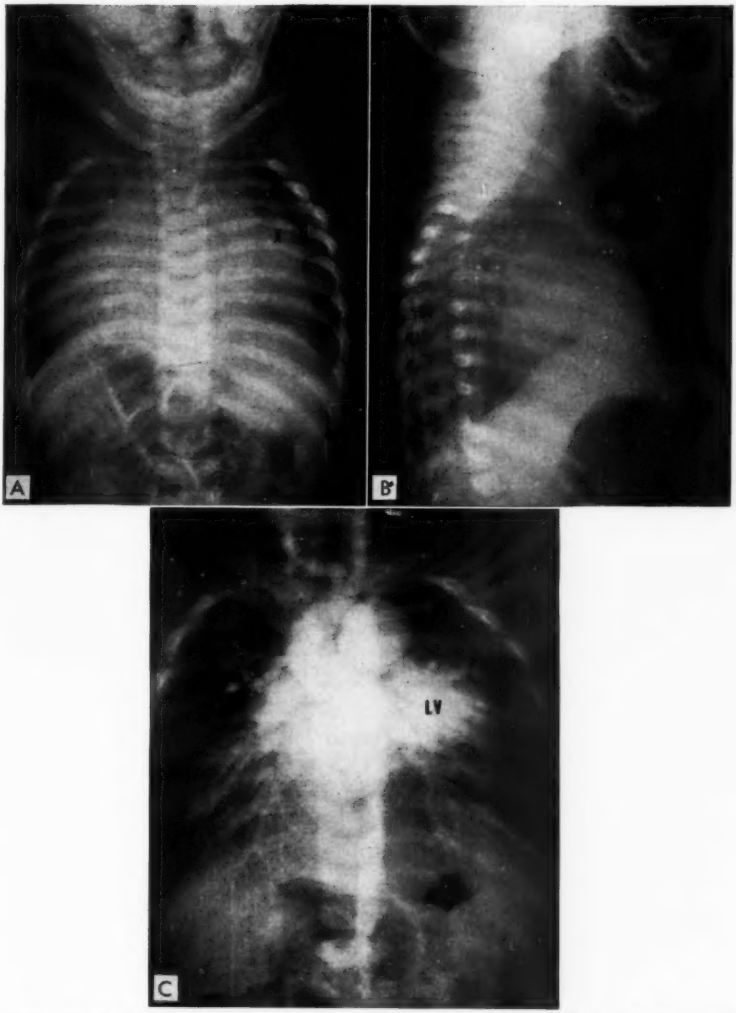


Fig. 17. An 11-month-old male infant with a harelip, cleft palate and abnormal feet, examined because of recurrent respiratory infections. *A*, Anteroposterior chest roentgenogram showing the heart apparently on the right and a mass on the left. The shadow in the left upper mediastinum was thought to represent the thymus gland (*X*). A situs inversus was postulated because of the apparent liver shadow on the left side of the abdomen. *B*, Lateral chest roentgenogram showing that apparently the mass is anterior. This is based on the fact that the mass is not posterior and hence must be lost in the cardiac silhouette. *C*, The heart sounds were heard best on the left side, and the electrocardiogram was normal. The stomach proved to be on the left side and appeared to be normal. An angiocardiogram proved the heart to be grossly normal, but displaced upward. The shadow believed to be the thymus gland is the left ventricle (*LV*). At operation bilateral diaphragmatic hernias through the foramina of Morgagni were found, with most of the liver up in the mediastinum.

Morgagni. These lesions may appear homogeneously dense, they may contain air, or they may show air and fluid levels. Figure 16 is a good example of a solid-appearing mass in the posteroanterior view containing air in the lateral view. There are times when the defect is so large that the liver arises above the level of the diaphragm. Under these circumstances the picture may be so confusing that an angiocardiogram is required to determine the position of the heart (Fig. 17).

MIDDLE MEDIASTINAL LESIONS

In infants and children lesions involving the lymph nodes are the most common mass lesions in the middle mediastinum. As is true whenever lymph nodes are involved in any part of the body, the enlargement will be due to tumor or infection.

Lymphomas

It is not the purpose of this clinic to discuss the various lesions which we tend to group under the term "lymphoma." From the differential diagnostic standpoint this is unimportant, since they all involve the more central tracheobronchial lymph nodes, giving rise to huge mass lesions which merge with the cardiac silhouette. These children are referred with surprising frequency to The Children's Hospital of Philadelphia with the admitting diagnosis of an enlarged heart. Figure 18 is a case of *lymphosarcoma* referred as a case of rheumatic fever. Often there is a pleural effusion adding to the confusion. Figure 19 is a case of *lymphatic leukemia* referred as "heart disease." It was not until the fluid was removed that the scalloped border of the nodal enlargement could be seen.

Hodgkin's disease is relatively rare in this age group compared with leukemia and lymphosarcoma. Figure 20 is a case of Hodgkin's disease which clearly shows the bilateral, irregular, confluent densities produced by lymph node enlargement.

Inflammatory Lesions of Lymph Nodes

Primary *tuberculosis* is the most common cause of inflammatory lymph node enlargement in infants and children. Usually it is the bronchopulmonary lymph nodes which are involved, rather than the more central tracheobronchial nodes. Primary tuberculosis is illustrated by Figure 21. The lesion is unilateral in contrast to the bilateral lymphoma lesions.

Sarcoidosis is rare in infants and children, but Figure 22 presents the

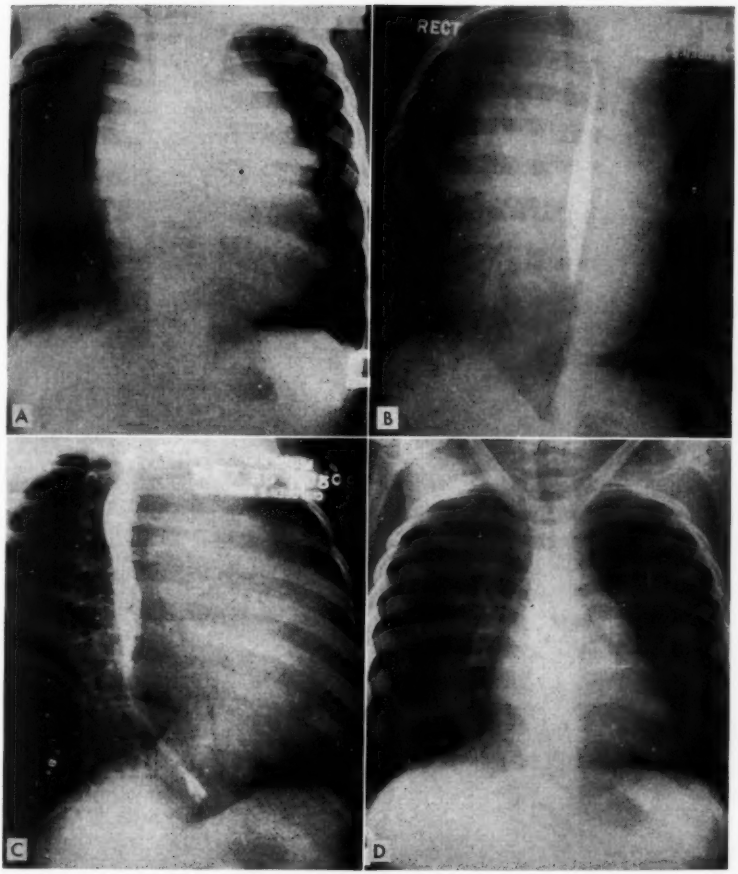


Fig. 18. A 9-year-old female child with a 4-month history of chest pain and fatigability was referred to the hospital with the diagnosis of rheumatic fever. Upon admission the girl had a mass in the neck which was biopsied and proved to be a lymphosarcoma. *A*, Posteroanterior chest roentgenogram showing a generalized enlargement of the mediastinum. The border is smooth, but is scalloped slightly in the middle on each side. *B*, Left anterior oblique view showing the mass lying in the middle of the mediastinum. *C*, Right anterior oblique view showing the mass lying in the middle of the mediastinum. *D*, The child received 1000 roentgens (tissue) to the mediastinum in 10 days. Posteroanterior chest roentgenogram taken 2 weeks after the x-ray treatment reveals that the mass has disappeared.

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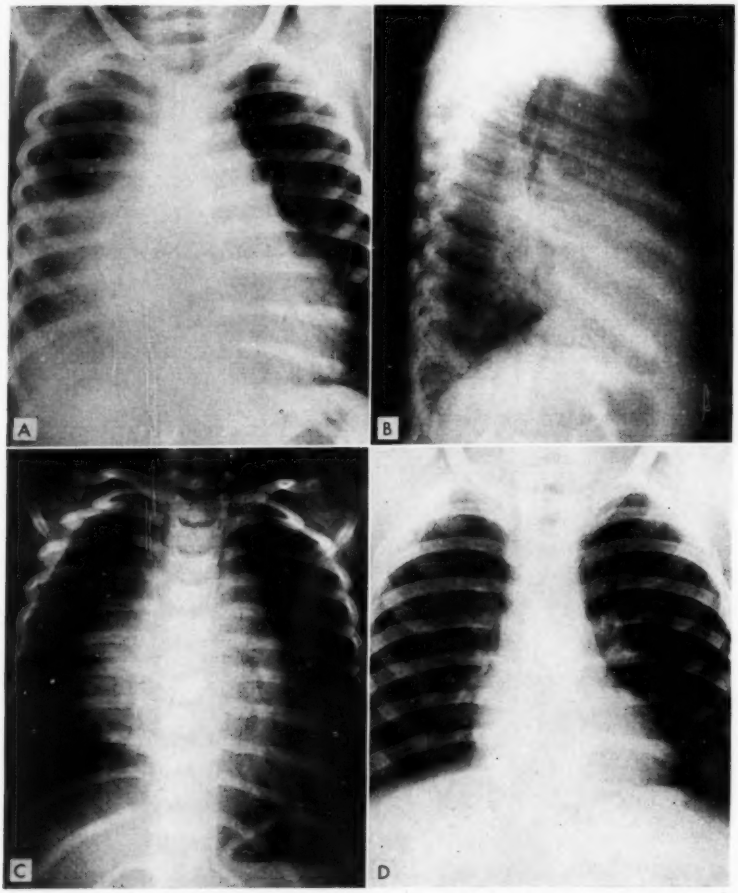
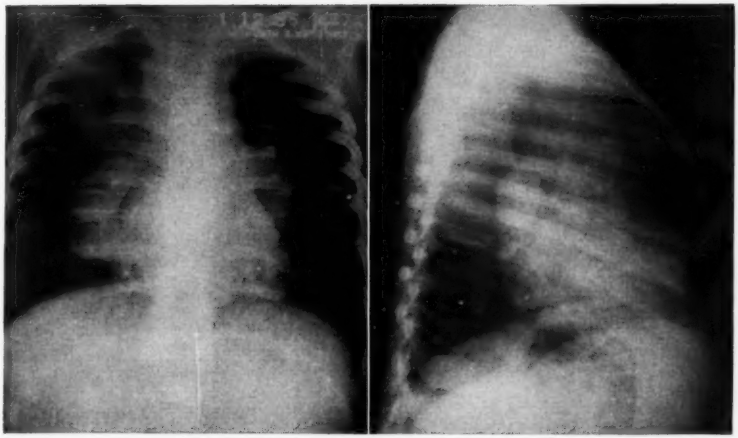
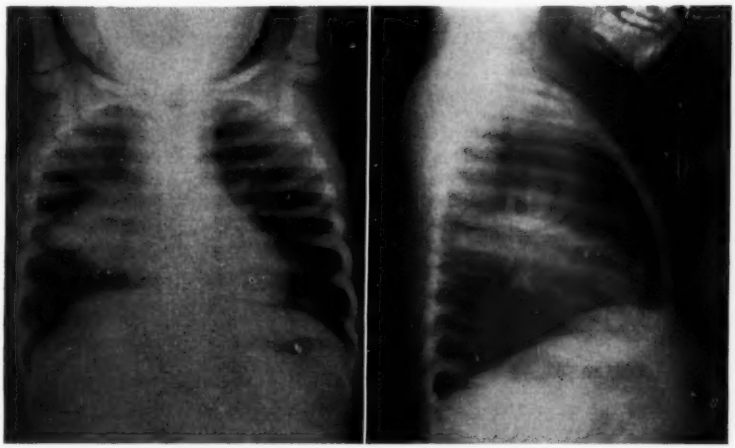


Fig. 19. A 5-year-old male child with a 6-week history of fever, sore throat and cough was referred to the hospital with the admission diagnosis of "heart disease." *A*, Posteroanterior chest roentgenogram showing an apparently large heart with a pleural effusion on the right side. It is easy to understand why the child was thought to have "heart disease." *B*, Lateral chest roentgenogram showing density in the hilar region with the fluid loculated anteriorly. *C*, Posteroanterior chest roentgenogram after removal of 160 cc. of fluid and introduction of 100 cc. of air. The nodular hilar adenopathy is now discernible. The child's peripheral blood revealed the diagnosis of lymphatic leukemia. *D*, Posteroanterior chest roentgenogram 1 month after 200 roentgens (air) had been delivered to the mediastinum. The hili are still slightly prominent, but the huge mass of adenopathy has disappeared.



A B

Fig. 20. A 9-year-old male child with a 1-month history of fever, cough and cervical adenopathy. Biopsy of a cervical lymph node resulted in the diagnosis of Hodgkin's disease. *A*, Posteroanterior chest roentgenogram revealing bilateral adenopathy of the central tracheobronchial nodes; *B*, lateral chest roentgenogram showing the masses lying in the middle mediastinum.



A B

Fig. 21. A 2-year-old female child was examined because of a chronic cough and a positive tuberculin test. *A*, Posteroanterior chest roentgenogram showing hilar adenopathy on the right, with the more peripheral bronchopulmonary nodes involved; *B*, lateral chest roentgenogram showing the hilar adenopathy and an inflammatory reaction in the apex of the right lower lobe. The child was treated for tuberculosis, and the chest findings gradually disappeared.

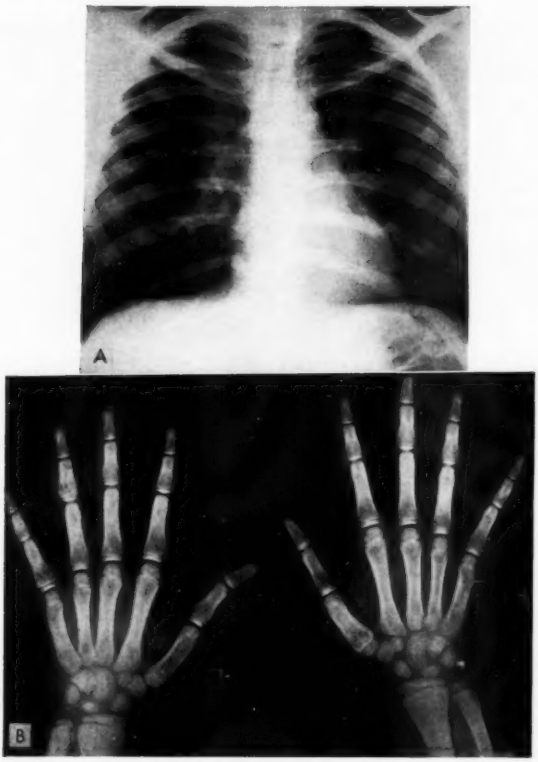


Fig. 22. A 10-year-old male child with a history of fever, generalized adenopathy, skin lesions, hyperglobulinemia and hypercalcemia was proved by skin and lymph node biopsy to have Boeck's sarcoidosis. *A*, Posteroanterior chest roentgenogram showing minimal hilar adenopathy on the right (arrow). As with all the inflammatory lesions, the bronchopulmonary nodes are the ones more often involved. *B*, Posteroanterior roentgenogram of the hands showing definite changes in several of the metacarpals and phalanges. Note also the soft tissue swelling around the middle phalanx of the third finger of the right hand.

bilateral lymph node enlargement of a case of sarcoidosis. Note the relatively clear space between the involved bronchopulmonary lymph nodes and the pericardium.

Aneurysms

The arch of the aorta lies within the middle mediastinum, and therefore an aneurysm of the arch would give rise to a mass lesion in this division. *Aneurysms of the aorta* are rare in infants and children. The Children's Hospital of Philadelphia has noted only one such case (Fig. 23).

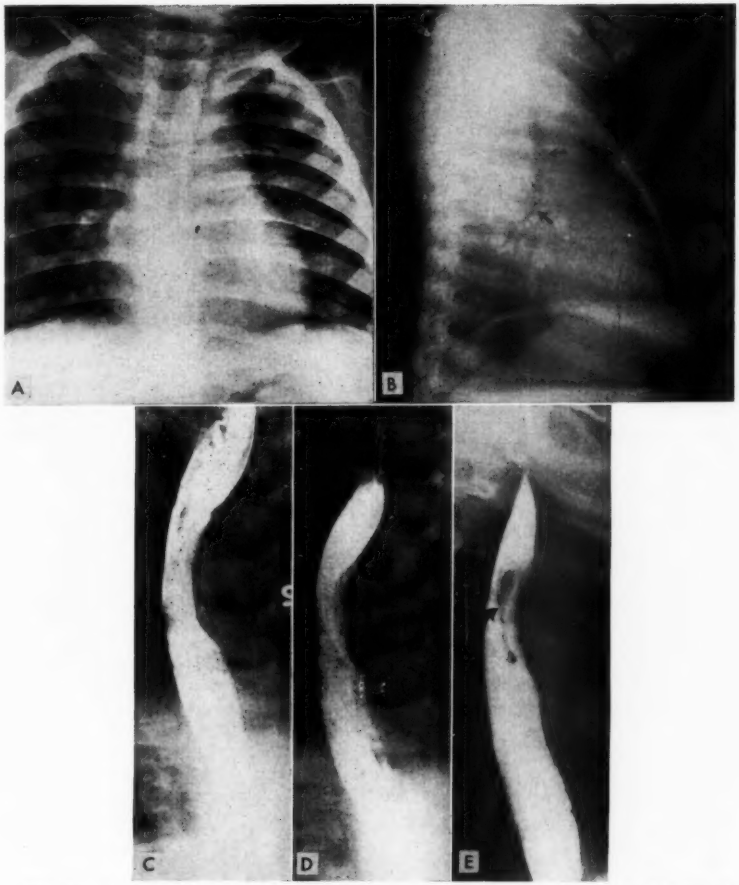


Fig. 23. A 22-month-old male infant entered the hospital with a 7-day history of hematemesis and passing blood clots per rectum. The bleeding was so extensive that the child was in shock and required transfusion. *A*, Posteroanterior chest roentgenogram showing a prominence in the region of the aortic arch (arrow); *B*, lateral chest roentgenogram showing the trachea displaced forward (arrows); *C*, anteroposterior view of barium-filled esophagus showing an abnormal deviation of the esophagus to the right at the level of the aortic arch; *D*, anteroposterior view of barium-filled esophagus showing the same deviation; *E*, lateral view of barium-filled esophagus showing a filling defect within the lumen at the level of the aortic arch (arrow). A diagnosis of an aortic aneursym with perforation into the esophagus was made, and the child was taken to surgery. During the induction of anesthesia the last remaining wall or thrombus gave way, and the boy suddenly bled to death. Autopsy proved a mycotic aneurysm with perforation into the esophagus.

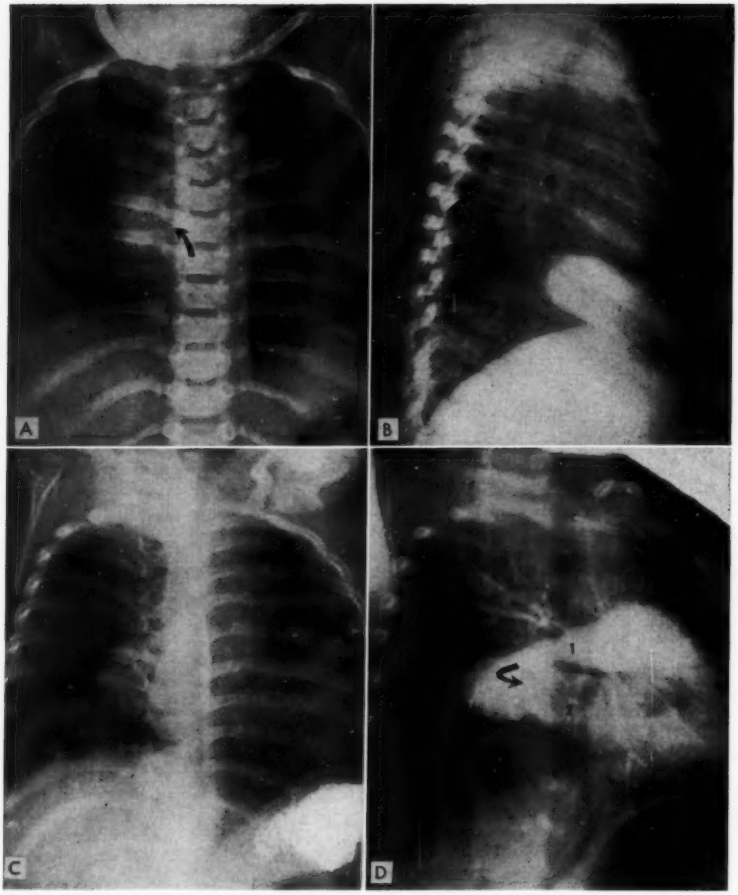


Fig. 24. A 9-month-old female infant with a history of cyanosis since birth and a gradually increasing heart size. *A*, Bucky anteroposterior chest roentgenogram showing a mass lesion in the hilus (arrow); *B*, lateral chest roentgenogram showing the mass lesion lying posteriorly (arrow); *C*, right anterior oblique chest roentgenogram showing the mass lesion with better definition; *D*, angiocardiogram in the right anterior oblique projection showing a pulmonary arteriovenous shunt with aneurysmal dilatation at the site of the communication (*1*, pulmonary artery; 2, pulmonary vein; the arrow indicates the direction of blood flow.)

Aneurysms of the pulmonary arteries are far more common in this age group than are those of the arch. Figure 24 is a pulmonary arteriovenous shunt with aneurysmal dilatation at the site of the communication. Actually, the mass lesion in this case lies in the posterior mediastinum, but the case is included with the middle mediastinal lesions

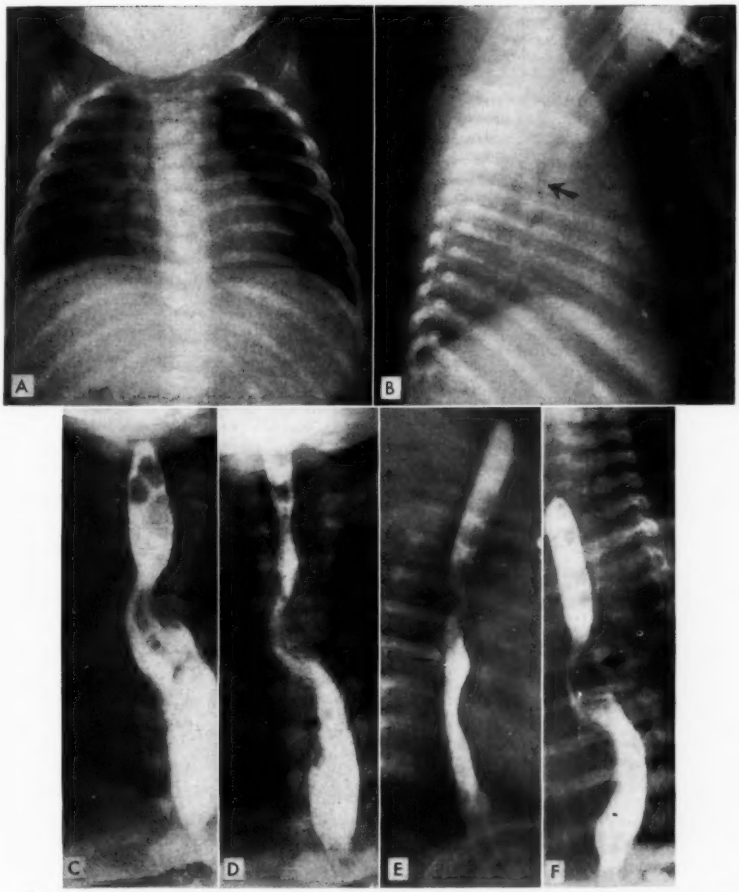


Fig. 25. A 3-month-old male infant was admitted because of wheezing, cyanotic episodes and a high-pitched cough since birth. *A*, Anteroposterior chest roentgenogram showing nothing abnormal except hyperventilation of both lung fields. *B*, Lateral chest roentgenogram showing constriction and posterior deviation of the trachea a short distance above the carina (arrow). *C*, Anteroposterior view of the barium-filled esophagus showing an upper indentation on the right (upper arrow) and a lower, larger indentation on the left (lower arrow). *D*, Anteroposterior view of the barium-filled esophagus with less barium within the lumen. This view shows the immense size of the lower left indentation. The upper indentation is produced by a right posterior aortic arch, and the lower indentation by a larger, left anterior aortic arch. *E*, Lateral view of barium-filled esophagus showing the posterior indentation (arrow) produced by the smaller posterior right aortic arch. *F*, Left anterior oblique view of barium-filled esophagus showing the large indentation produced by the anterior left aortic arch (arrow). At operation the smaller posterior arch was divided.

because the dilated pulmonary artery and vein are in the middle mediastinum, and only the aneurysmal dilatation lies posteriorly.

Congenital Anomalies of the Great Vessels

A *double aortic arch* can hardly be classified as a mass lesion of the middle mediastinum, but, as shown in Figure 25, the trachea can be displaced to such a degree that a mass lesion might be suspected. By carrying out a test of swallowing function, the true basis of the lesion can be understood. Therefore, whenever a mass lesion of the mediastinum is suspected, a test of swallowing function is always indicated.

POSTERIOR MEDIASTINAL LESIONS

Neurogenic Tumors

As indicated above, nearly all neurogenic tumors of the mediastinum have their origin from the paravertebral sympathetic nerve trunks and the intercostal nerves, and therefore are not true mediastinal mass lesions. Since, however, all these tumors grow into the mediastinum, they are classified as posterior mediastinal neoplasms. Except for the normal thymus gland, which is not a neoplasm, neurogenic tumors are the most frequent mass seen by roentgen examination in the mediastinum. In adults the neurilemmoma and the neurofibroma are the most common of these neurogenic lesions, but in infants and children the most common is some form of neuroblastoma.

Since *neuroblastomas* are discussed elsewhere in this symposium (p. 449), it is not the purpose here to give a pathologic account of this interesting tumor. Suffice it to say that these tumors vary from an extremely malignant embryonic type of sympathicoblastoma to a benign adult type of ganglioneuroma. Sometimes elements of each are present in the same tumor. It is said that neuroblastomas have a predilection for the upper third of the posterior mediastinum, but they are also common in the lower posterior mediastinum. It is wrong, therefore, to use any specific location in the posterior mediastinum as an aid in differential diagnosis. The neuroblastoma sometimes has an irregular, nebulous periphery in contrast to the smooth, definite edge of the ganglioneuroma. Calcification is frequently present within the neuroblastoma, and it is usually described as being finely scattered within the lesion. In our experience this differential point is wrong, since the calcification in neuroblastomas may take on any form (Fig. 26). The calcium present in these lesions is simply the end stage of a mass growing beyond its blood supply, with subsequent necrosis and calcification. Occasionally one of these tumors will send out a dumbbell-like extension

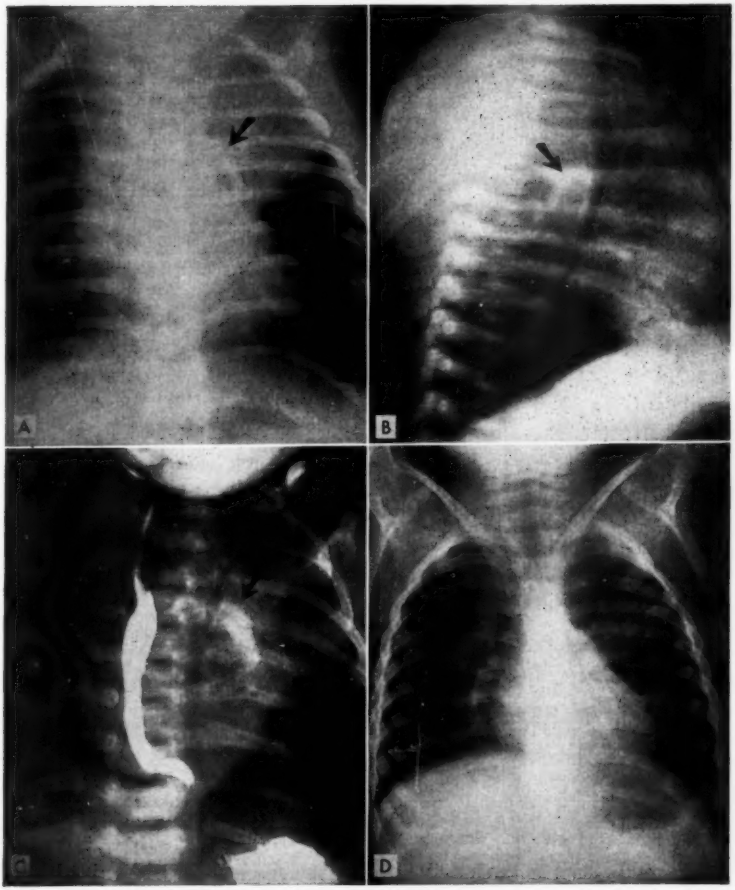


Fig. 26. A 7-week-old male infant entered the hospital for repair of an inguinal hernia and was found to have a lymph node in the left cervical region. This finding resulted in a roentgen examination of the chest. *A*, Anteroposterior chest roentgenogram showing a large area of density in the left upper chest. Within the homogeneous density a curvilinear calcification is present (arrow). *B*, Lateral chest roentgenogram showing the mass lesion to be in the posterior mediastinum with some anterior deviation of the trachea. The calcification appears to be in the shape of a horseshoe (arrow). *C*, Anteroposterior view of barium-filled esophagus which shows the large size of the mass lesion more graphically. The calcification is more clearly visualized (arrow). At operation the lesion proved to be a neuroblastoma. It was entirely excised. *D*, Posteroanterior chest roentgenogram 5 years later showing a normal chest.

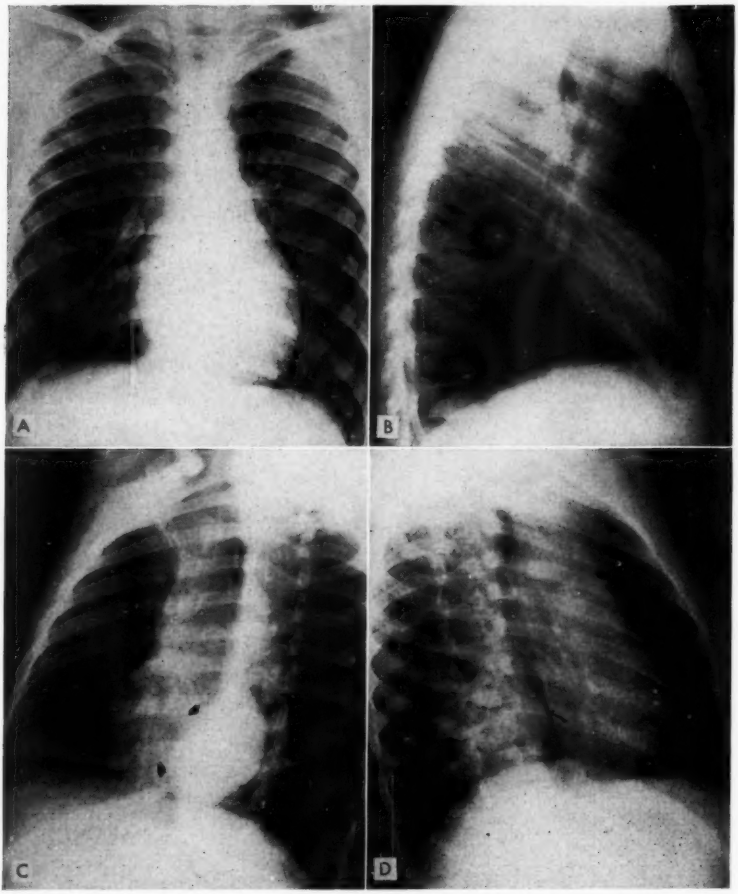


Fig. 27. A 7-year-old boy was admitted to the hospital because of pain in the left upper quadrant, ataxia and weakness of the legs of 1 month's duration. *A*, Posteroanterior chest roentgenogram showing a paravertebral mass lesion superimposed upon the right cardiac silhouette (arrow); *B*, lateral chest roentgenogram which fails to reveal anything abnormal; *C*, left anterior oblique chest roentgenogram clearly showing the mass lesion superimposed on the cardiac shadow (arrow); *D*, right anterior oblique chest roentgenogram showing the paravertebral lesion behind the heart (arrow). A myelogram revealed a complete block at the level of D 11. At operation the lesion proved to be a neuroblastoma with extension into the spinal canal.

through an intervertebral foramen and compress the cord. Figure 27 is a good example of a paravertebral neuroblastoma in a patient admitted to the hospital because of neurologic findings in the lower extremities. Myelography revealed cord pressure, and subsequent surgery proved the presence of the tumor within the spinal canal. Overexposed Bucky

films will sometimes demonstrate the enlarged intervertebral foramina and the widening of the rib interspaces posteriorly. In our experience these bone changes are seldom seen, even with the proper technique.

Ganglioneuromas, because of their benign quality, are often large before they give rise to symptoms (Fig. 28).

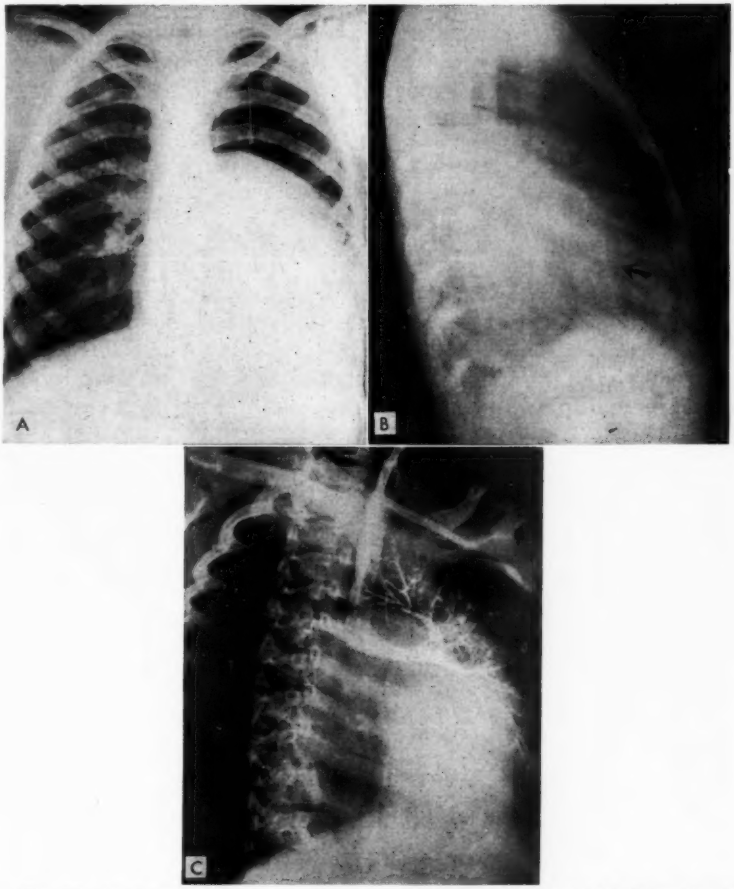


Fig. 28. An 8-year-old boy was admitted to hospital with an initial diagnosis of pneumonia, but the consolidation failed to respond to sulfonamides. *A,* Postero-anterior chest roentgenogram showing a huge mass lesion filling the left lower chest. The smooth-bordered mass completely hides the left cardiac border. *B,* Lateral chest roentgenogram showing the mass lesion in the posterior mediastinum (arrows). *C,* Right anterior oblique view of a bronchogram showing elevation and lateral deviation of the left lower lobe bronchus. At operation the lesion proved to be a ganglioneuroma. The patient is now 20 years old and well.

Duplications of the Foregut

The second most common posterior mediastinal mass lesion encountered in infants and children is the *gastroenteric cyst*. These duplications of the foregut may be lined with a primitive esophageal epithelium, gastric mucosa, intestinal mucosa, and sometimes with a mixture of several different types of gut epithelium. These fluid-filled cysts are usually immense by the time they produce symptoms and have a perfectly smooth outline in contrast to the neurogenic tumors, which tend to show some irregularity. There may be a persisting stalk passing down through the diaphragm and connecting with the intestine (Fig. 29), or the cyst may lie in the posterior mediastinum entirely separate from the gastrointestinal tract (Fig. 30).

Neurenteric Cysts

In the previous paragraph gastroenteric cysts were discussed as being duplications of the foregut with or without a stalk connecting them with the gastrointestinal tract. Similar cysts, but less common, are those of neurenteric origin. This cyst has a wall histologically resembling some segment or segments of the foregut, and a connecting stalk to the meninges and spinal cord through a tunnel-like defect in the vertebral

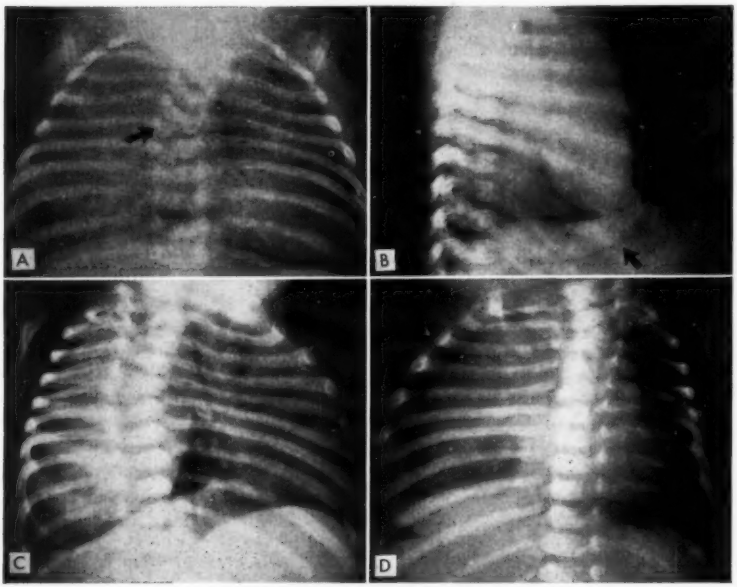


Fig. 29. (*Legend on page 405.*)

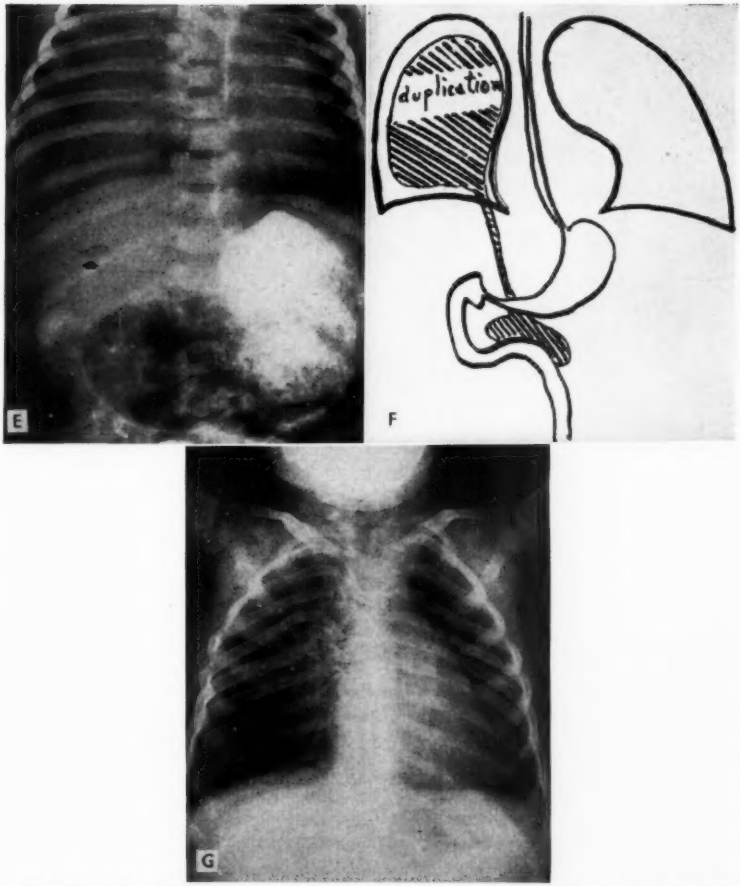


Fig. 29. A 2-month-old male infant was examined because of shortness of breath of 24 hours' duration. *A*, Anteroposterior chest roentgenogram showing a huge mass lesion filling the right side of the chest. There is a hemivertebra in the mid-dorsal region (arrow) causing a scoliosis. *B*, Lateral chest roentgenogram showing the mass lesion lying posteriorly. From this lateral view the lesion actually appears to be in the middle mediastinum, but this is superimposition of the anterior portion of the mass on the cardiac shadow. The arrow shows the inferior border of the mass, which extends posteriorly to the spine. *C*, Right anterior oblique chest roentgenogram showing the mass to be posterior. *D*, Left anterior oblique chest roentgenogram showing the mass to be posterior. *E*, Anteroposterior chest roentgenogram with barium in the esophagus showing the esophagus to be displaced to the left. A bubble of air seems to lie in the middle of the liver (arrow). *F*, At operation the mass proved to be a huge duplication cyst of the foregut with a stalk passing down through the diaphragm and originating from the fourth portion of the duodenum and the duodenojejunal junction. *G*, Posteroanterior chest roentgenogram taken 2 years later showing a normal chest except for the scoliosis.

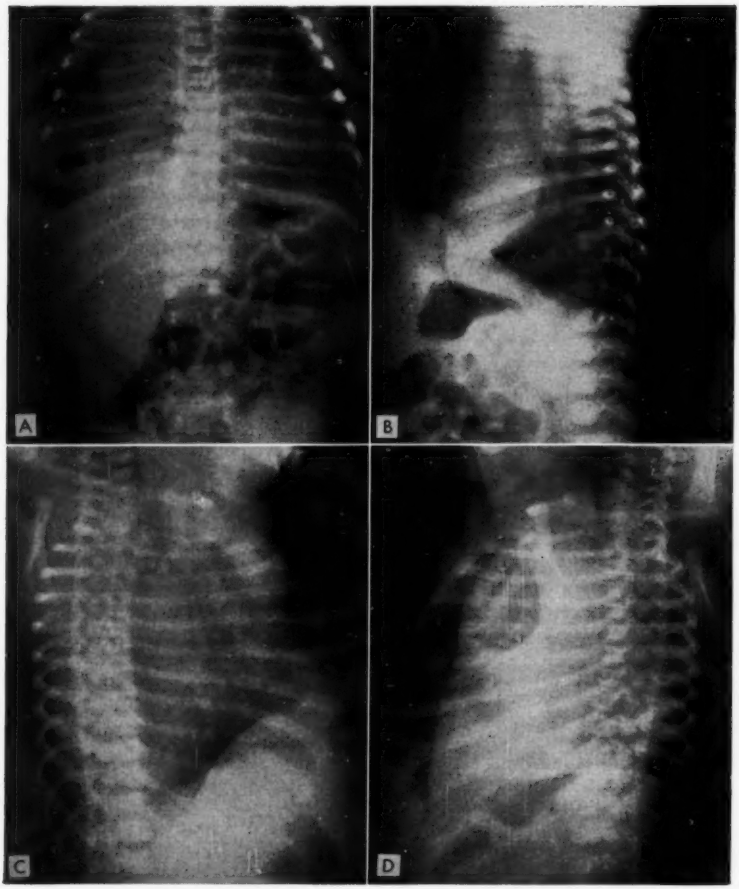


Fig. 30. A 5-week-old male infant brought for examination because for 2 days his head had been turned to the right. *A*, Anteroposterior chest roentgenogram showing a huge mass filling the right side of the chest; *B*, lateral chest roentgenogram showing, as in Figure 29, *B*, the mass lesion apparently in the middle mediastinum; *C*, right anterior oblique view showing the mass lesion to be posterior; *D*, left anterior oblique view showing the mass lesion to be posterior. At operation a duplication cyst of the foregut was removed. No stalk connected the lesion with the gut. The cyst was lined with jejunal mucosa.

bodies. Roentgenologically, this lesion is characterized by a defect in the anterior aspect of the spine with a faulty formation of the vertebrae and a mediastinal soft tissue mass. The mass may be continuous with a giant diverticulum or duplication of the intestinal tract and sometimes is associated with a diaphragmatic hernia.

Bronchogenic Cysts

Bronchogenic cysts probably develop from accessory respiratory buds which originate from the primitive foregut, or they may be pinched from the tracheobronchial tree after it has arisen as a diverticulum from

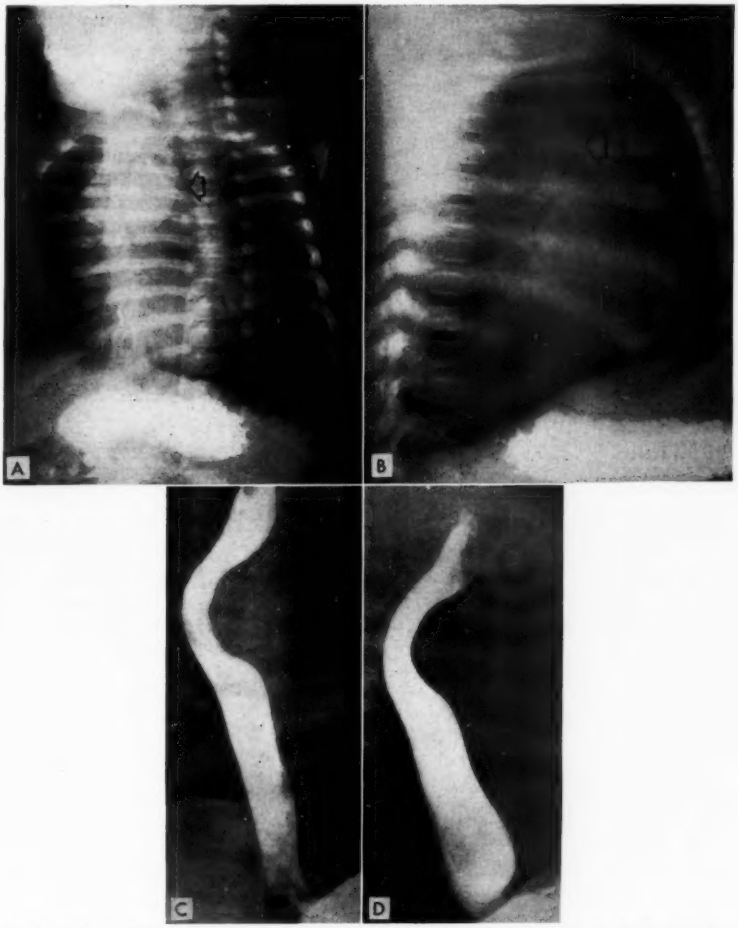
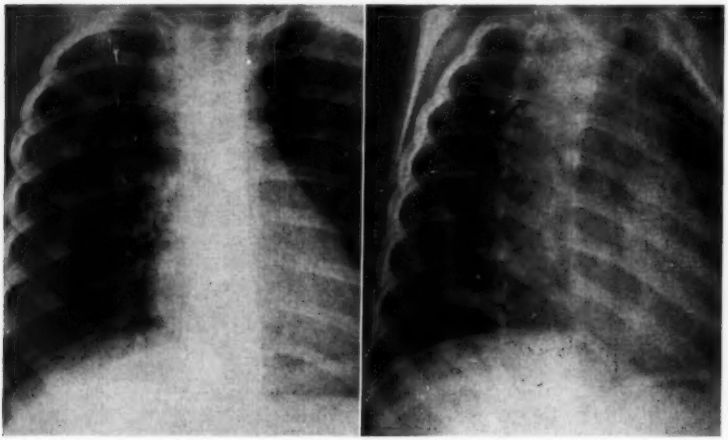


Fig. 31. A 10-week-old male infant with dyspnea since birth. *A*, Left anterior oblique chest roentgenogram showing a mass lesion just below the carina (arrow); *B*, lateral chest roentgenogram showing anterior deviation of the trachea (arrow); *C*, anteroposterior view of barium-filled esophagus showing extreme deviation of the esophagus to the right just above the level of the carina; *D*, lateral view of barium-filled esophagus showing posterior deviation of the esophagus just above the level of the carina. At operation a bronchogenic cyst was removed.

the foregut. They are lined by pseudostratified ciliated columnar epithelium, and the walls usually contain smooth muscle and occasionally cartilage. They are filled with a milky mucoid material, or may partially drain and contain air. Maier[8] classified these cysts into four groups on the basis of their location: (1) *paratracheal,* in which the cysts are attached to the tracheal wall, usually on the right just above the bifurcation; (2) *carinal,* in which the cysts are attached to the carina-trachea and often to the anterior esophageal wall as well; (3) *hilar,* in which



A B

Fig. 32. A 4-year-old girl complained of almost constant upper respiratory tract infections of 2 years' duration. A, Posteroanterior chest roentgenogram showing a paratracheal mass lesion on the right (arrow); B, right anterior oblique view better defining the paratracheal mass lesion (arrow). At operation a bronchogenic cyst was removed.

the cysts are attached to one of the main or lobar bronchi; and (4) *paraesophageal,* in which the cysts are in intimate relationship with the esophagus, may even lie within its wall, and have no connection with the tracheobronchial tree.

In the older child or the adult the majority of bronchogenic cysts belong to the hilar group and are discovered as an incidental finding. Carinal bronchogenic cysts often cause severe respiratory obstruction; consequently these cysts are found in early infancy (Fig. 31). Paratracheal bronchogenic cysts usually do not cause enough obstruction to produce symptoms in early infancy, but often just enough obstruction to produce frequent upper respiratory tract infections (Fig. 32).

Lesions of the Esophagus

Achalasia (cardiospasm), although not common in the age group under discussion, may give rise to a posterior mediastinal shadow which may be confusing in plain films (Fig. 33). Again, as with most of the mediastinal mass lesions, a test of the swallowing function will facilitate the diagnosis.

Paraesophageal and *esophageal hiatal hernias* may often produce a

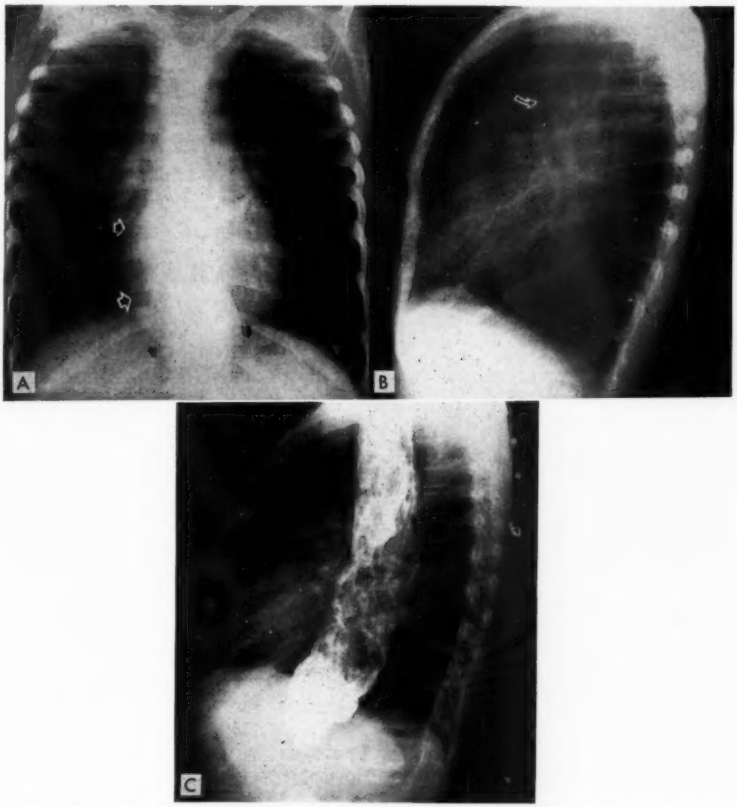
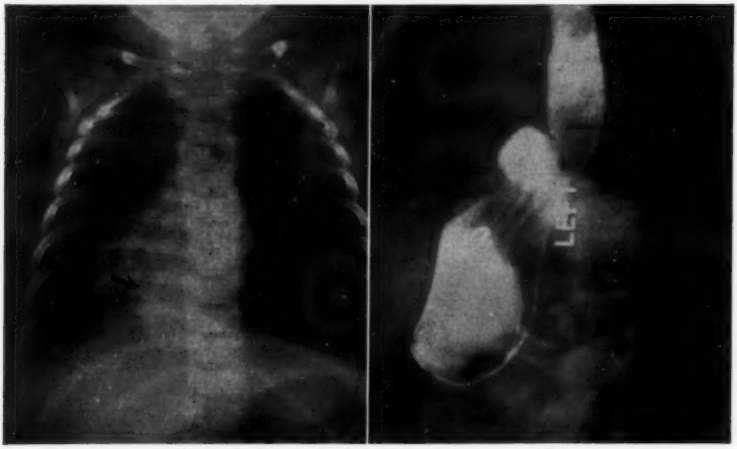


Fig. 33. A 12-year-old boy examined because of a chronic cough. *A*, Posteroanterior chest roentgenogram showing a mass lesion in the midline superimposed on the cardiac silhouette (arrows). Note how the mass extends below the lower heart border. *B*, Lateral chest roentgenogram showing the mass posterior to the trachea and causing anterior deviation of the trachea (arrow). *C*, Lateral chest roentgenogram with a barium-filled esophagus showing the mass to be the classic dilated esophagus of achalasia.



A B

Fig. 34. A 3-month-old male infant with a complex type of cyanotic congenital heart disease associated with dextrocardia and asplenism. *A*, Anteroposterior chest roentgenogram with a small mass lesion superimposed on the cardiac silhouette (arrow); *B*, anteroposterior view of barium-filled esophagus and stomach showing a paraesophageal hernia to be the cause of the small mass lesion.

density in the posterior-inferior mediastinum which is confusing until the swallowing function test clarifies the problem (Fig. 34).

Diaphragmatic Hernias

A typical diaphragmatic hernia through the foramen of Bochdalek with air-filled loops of bowel in the chest presents no problem in differential diagnosis. At times, however, a solid mass of liver, spleen or kidney may present through the hernia. Figure 35 is such a case in which suspicion was raised from the plain films that the mass might be the right kidney, and an intravenous urogram confirmed the diagnosis.

Mediastinal Meningoceles

Posterior meningoceles are common in infants, but intrathoracic meningoceles are rare. The possibility should always be kept in mind, however, when a defect in the anterior aspect of the spine is accompanied by a posterior mediastinal mass lesion. Myelography will establish the communication between the subarachnoid space and the mediastinal mass. This is the differential point between intrathoracic meningoceles and neuroenteric cysts, since no communication is found with the neuroenteric cysts.

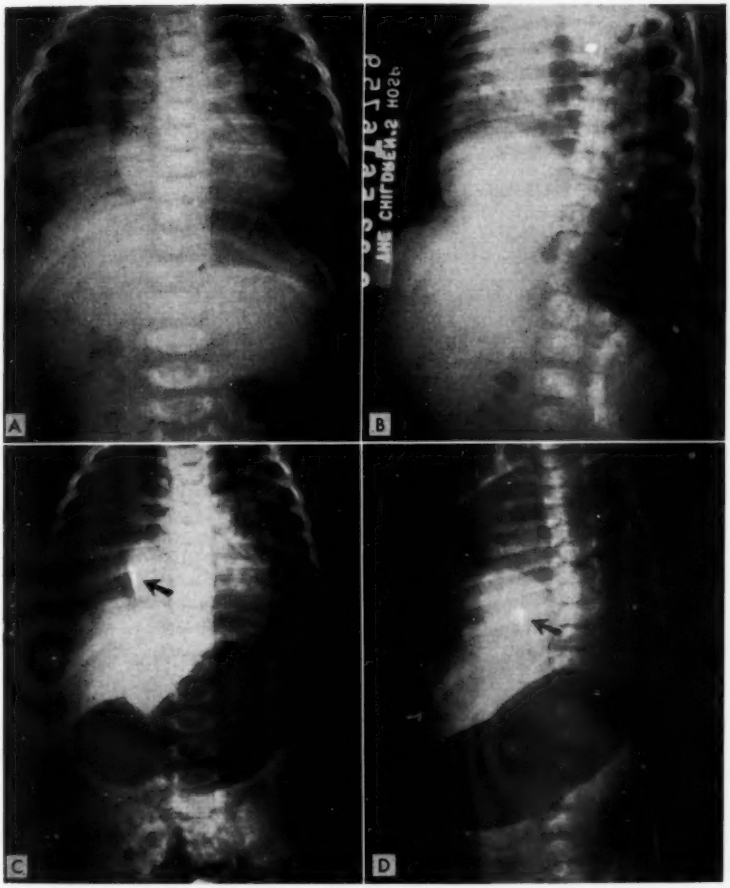


Fig. 35. A 5-month-old male infant referred for evaluation of a cardiac murmur. A, Posteroanterior chest roentgenogram showing a large mass lesion in the right cardiophrenic angle. B, Left anterior oblique view showing the mass lesion to be posterior. C, Anteroposterior view of an intravenous urogram showing the mass lesion to be the right kidney (upper arrow). The lower arrow points to the normal left kidney. D, Left anterior oblique view of an intravenous urogram showing the right kidney with better definition (arrow). At operation the right kidney entered the chest through the right foramen of Bochdalek.

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1740 Bainbridge Street
Philadelphia 46, Pa.

TUMORS OF THE GASTROINTESTINAL TRACT AND PANCREAS

BENJAMIN H. LANDING, M.D.

LESTER W. MARTIN, M.D.

Tumors of the mouth, tongue and pharynx are discussed elsewhere (p. 369), and tumors of the esophagus, stomach, small intestine, appendix, colon and pancreas, in this order, in this clinic.

GENERAL CONSIDERATIONS

With the exception of colonic polyp, no tumor of the gastrointestinal tract can be considered common in children. Nevertheless both malignant and benign varieties have been reported from every segment of the gastrointestinal tract of infants and children. Such tumors are rare in the newborn group, their frequency increasing proportionately with the age of the patient throughout life.

Approximately 1 to 5 per cent of all tumors seen in the pediatric age group arise from the gastrointestinal tract.[31, 32]

Excluding colonic polyps and duplications, tumors arising in the gastrointestinal tract in children are frequently malignant[31, 32] and from a clinical standpoint must always be considered so until proved otherwise (Table 1).

Clinically, tumors of the gastrointestinal tract generally present with either a palpable mass, pain, bleeding or intestinal obstruction. Admittedly, such tumors are an infrequent cause of any one of these, but must be considered by the clinician in each instance (Tables 2, 3).

From the Divisions of Pathology, Pediatrics and Surgery of the Children's Hospital and Children's Hospital Research Foundation, and the University of Cincinnati College of Medicine, and from the Schoepf Clinic for the Study and Treatment of Cancer in Childhood, of the Children's Hospital, Cincinnati.

Tumors of the small intestine frequently present as intussusception with obstruction and pain.[8, 10, 17]

Because of their importance in differential diagnosis of tumors of the stomach and intestine, it seems of value to present some statistics concerning the frequency of duplications at different levels of the gas-

TABLE 1. *Tumors of Gastrointestinal Tract and Pancreas in Combined Autopsy and Surgical Material of Cincinnati Children's Hospital, 1940–58*

Stomach:	
Neuroblastoma	1
Ectopic pancreas	1
Small intestine:	
Ectopic pancreas	6
Malignant lymphoma	4
Sarcoma	1
Appendix:	
Carcinoid	5
Hemangioma	1
Malignant lymphoma	1
Colon:	
Hemangioma	2
Malignant lymphoma	4
Polyp	33
Pancreas (pseudocyst)	1

TABLE 2. *Analysis of 67 Palpable Abdominal Tumors in Children, Excluding Hydronephrosis*[31]

Wilms' tumor	23	
Neuroblastoma	16	
Others:	28	
Liver	7	
Ovary	6	
Kidney and adrenal	5	
Retroperitoneal teratoma	1	
Mesothelioma	1	
Embryonal sarcoma	2	(1 of duodenum)
Mesenteric lymphangioma	2	
Malignant lymphoma	4	(2 of ileum, 1 of cecum)

trointestinal tract[17] and the sites of origin of abdominal cysts.[18] These data are given in Tables 4 and 5.

Tumors of the gastrointestinal tract are exceedingly rare in the newborn period. Potter's[40] series of malignant tumors present at birth includes five patients with neuroblastoma, two with Wilms' tumor and two with leukemia, but no tumor of the stomach or intestine. Longino's[32] series of abdominal masses in newborn infants includes one

TABLE 3. *Causes of Gastrointestinal Hemorrhage in Infants and Children, 246 Cases*[20]

Ulcerative colitis	94	**Meckel's diverticulum**	17
Cause undetermined	19	**Volvulus**	6
Esophageal varices	10	**Ileal band**	1
Regional enteritis	5	**Blood dyscrasias**	12
Acute enteritis	1	**Mesenteric adenitis**	5
Gastroenteritis	2	**Foreign body**	5
Gastric ulcer	1	**Colonic polyp**	40
Duodenal ulcer	8	**Jejunal polyp**	1
Meningitis	2	**Malignant lymphoma**	1
Intussusception	17	**Rectal carcinoma**	1

malignant leiomyosarcoma of the colon. Others have reported single cases of hemangioendothelioma,[5] angiosarcoma of the small intestine[58] and leiomyosarcoma of the jejunum[44] in newborn infants.

Among the few reported instances of transmission of malignant tumor from mother to fetus in utero, malignant melanoma, malignant lymphoma and bronchogenic carcinoma have been included, but gastrointestinal tract tumors have apparently not been observed.[23]

ESOPHAGUS

Benign tumors which have been reported in the esophagus and may be found in children include leiomyoma, fibroma, hemangioma and polyp, as well as duplication, the last being by far the most frequent (Tables 4, 5). Any of these lesions may cause dysphagia, obstruction or bleeding, and the duplications must be distinguished from other types of mediastinal cyst.[47] Stout and Lattes[50] report a newborn infant with "juvenile fibromatosis" involving many organs, including the esophagus, as well as a cartilage nodule in the wall of the esophagus in a 19-year-old patient, and an instance of a nodule of ectopic thyroid in the wall of the esophagus. All cases of esophageal polyp reported by Stout occurred in

TABLE 4. *Site of Origin of Duplications of the Gastrointestinal Tract, 68 Cases*[17]

Base of tongue	1	**Ileum**	19
Esophagus	13	**Ileocecal valve**	8
Small intestine (intrathoracic)	3	**Cecum**	3
Stomach	2	**Sigmoid**	2
Duodenum	4	**Rectum**	3
Jejunum	4	**Double colon or rectum**	4

TABLE 5. *Site of Origin of Abdominal Cysts, 47 Cases*[18]

Ovary	22	**Duplications:**	4
Mesentery	13	**Ileum**	1
Omentum	5	**Cecum**	2
Pancreas	3 (2 pseudocysts)	**Rectum**	1

adults, and he feels that the rare papillomas of the lower third of the esophagus described in children are inflammatory in origin.

Local resection and end-to-end anastomosis of the esophagus are generally feasible for the isolated benign esophageal tumor.

Malignant tumors which may arise in the esophagus include squamous carcinoma, adenocarcinoma, leiomyosarcoma, rhabdomyosarcoma, malignant lymphoma, carcinosarcoma and malignant melanoma. The writers have not observed a malignant tumor primary in the esophagus in a child, nor have they found a convincing report of such an occurrence. Of the tumor types listed, malignant lymphoma and leiomyosarcoma seem most liable to occur in children. The writers have observed an eight-year-old child with esophageal obstruction and dysphagia resulting from leukemic infiltration. It is worth mentioning that leiomyoma of the gastrointestinal tract is commonly misdiagnosed as fibroma, neurofibroma or neurilemmoma, and comparable mistakes are often made for leiomyosarcoma.[49]

The frequency of carcinoma of the esophagus is increased in patients with *lye stricture*, and possibly also in those with sulfuric acid stricture, although the writers have not found data on the latter point. Kiviranta[28] reported 9 carcinomas of the esophagus in 381 patients with lye stricture, a frequency of 1000 times random. The average age of these patients was 43, with the latent period at least 24 years, so that esophageal malignancy on this basis need not be expected in children, but the matter is of concern to pediatricians from the preventive point of view. Some writers feel that carcinoma of the esophagus also occurs with increased frequency in patients with *achalasia*, but conclusive data are not available.

With the possible exception of some cases of malignant lymphoma, the preferred treatment of all tumors of the esophagus in children is surgical. Local resection with end-to-end anastomosis of the esophagus is generally possible for isolated benign esophageal tumor. Gastrostomy may be of value in the palliative treatment of obstructing lymphoma or other malignant tumors of the esophagus.

STOMACH

Tumors of the stomach are both more frequent, and of a wider variety of cell types, than those of the esophagus. Benign tumors reported in the stomach include adenomatous polyp, carcinoid, ectopic pancreas, leiomyoma, granular cell myoblastoma, hemangiopericytoma, glomus tumor, lymphangioma, lipoma, neurofibroma, neuroma (in the beds of chronic ulcers), inflammatory polyp, eosinophilic granuloma, and teratoma.[11, 49] Any of these may occur in a child, but leiomyoma and ectopic pancreas are probably the most common. Microscopic points of interest

are that Brunner's glands are often seen in association with "pancreatic adenoma" of the stomach, and that leiomyoma does not have a capsule, in contrast to neurilemmoma, with which it is easily confused. Assessment of the degree of malignancy of gastric leiomyoma is difficult, and malignancy is often underestimated microscopically, so that any gastric leiomyoma should be regarded with suspicion. Some gastric polyps in older children probably result from the Peutz-Jeghers syndrome (see p. 418).

Malignant tumors described as arising in the stomach include carcinoma, carcinoid, leiomyosarcoma, rhabdomyosarcoma, neuroblastoma, malignant lymphoma, Hodgkin's disease, plasmacytoma and Kaposi's disease, the third, fourth, fifth and sixth of which may be expected on occasion in children. Of the three basic patterns of gastric carcinoma (mucus cell carcinoma, pylorocardiac gland carcinoma and intestinal cell carcinoma), the first has the youngest average age of onset[37] and is perhaps the type occasionally reported in children,[11] most commonly in the pyloric region. Mulligan and Rember[37] state that mucus cell carcinoma of the stomach is 98 per cent lethal, and question the value of radical surgery.

The clinical features of tumors of the stomach include vomiting, abdominal pain, "dyspepsia," hematemesis, rarely perforation and occasionally palpable mass. The writers have seen a 12-year-old boy with symptoms highly suggestive of peptic ulcer, caused by a nodule of ectopic pancreas in the prepyloric region, with no actual ulceration. The behavior of leiomyosarcoma of the stomach has been surveyed by Giberson et al.[14] Of 40 patients ranging in age from 10 to 73 years, 19 had a mass, 19 gross bleeding, 3 chronic bleeding, 11 pallor, 20 weight loss and 30 abdominal distress. Ulceration was present in 23 tumors, and evidences of healed ulceration in 7 more. None of the tumors occurred in the pyloric region or in the upper fundus, and only 18 metastasized, none outside the abdomen. These writers feel that surgery is indicated even if metastases are present, and found a 5-year survival rate of 54 per cent in their series. The case of a 3½-year-old girl, with anorexia and hematemesis caused by gastric leiomyosarcoma is discussed from clinical, radiologic and pathologic points of view in the 1957 Cancer Seminar of the Penrose Cancer Hospital,[55] and the authors have observed a 2½-year-old girl with a gastric leiomyosarcoma treated by radical surgery, who was asymptomatic 3 years later.

Again with the possible exception of some patients with malignant lymphoma or Hodgkin's disease, surgery is the recommended treatment for all gastric tumors. Differential diagnosis includes trichobezoar, lesions of the spleen and the several types of abdominal tumors and cysts listed in Tables 2, 4 and 5.

For completeness' sake, the pyloric "tumor" of hypertrophic pyloric

stenosis should be mentioned, but the early onset and typical clinical picture easily distinguish this condition from the neoplasms discussed above.

Treatment of tumors of the stomach must be radical; however, it must be borne in mind that the stomach is in some way necessary for normal growth.[17] It would seem advisable, therefore, to preserve as much stomach as possible in each instance. Since carcinoma is rarely seen in growing children, and leiomyosarcoma is generally not highly malignant, it is usually possible to preserve at least a significant portion of the stomach.

SMALL INTESTINE

With the exception of malignant lymphoma, tumors of the small intestine in children rarely present as palpable masses, and the clinical aspects are usually abdominal pain or "colic," or the features of intestinal obstruction (distention, vomiting, constipation or diarrhea). Intussusception occurs with some frequency,[11, 19] but volvulus and perforation are rare, and hemorrhage is rare except with hemangioma. The differential diagnosis of small intestinal tumors includes intestinal tuberculosis, gastroenteritis, appendicitis, other causes of obstruction, intussusception, volvulus, perforation or hemorrhage (Table 3) and the other types of abdominal masses listed in Tables 2, 4 and 5. Benign tumors reported to occur in the small intestine, any of which may occur in children, include polyp, and adenoma, hemangioma, lymphangioma, leiomyoma, carcinoid and lipoma. Multiple lipomas of the small intestine occur (diffuse nodular submucosal lipomatosis), but the writers have not found a report of this condition in a child. The findings in a 6-month-old infant who died of intra-abdominal hemorrhage due to diffuse hemangioma of the mediastinum, diaphragm, mesentery, small intestine and colon are presented in the fascicle on Tumors of the Cardiovascular System.[30] MacCollum[33] reports a 16-year-old girl with 16 separate hemangiomas of the small and large intestines which were resected because of gastrointestinal bleeding.

Probably most children with adenomas or polyps of the small intestine are instances of the *Peutz-Jeghers syndrome*,[26] a hereditary (mendelian dominant with incomplete penetrance) disorder characterized by polyposis of the gastrointestinal tract, and pigmented (melanin) spots of the oral mucosa, face, hands and feet. Polyps of the stomach in this condition are rare, and small intestinal involvement is the most typical manifestation. Pain, vomiting and recurrent obstruction or intussusception are the typical abdominal symptoms.[62] When the colon is involved, there are fewer polyps than in hereditary multiple polyposis of the colon, and the clinical findings are melena, rectal prolapse and rarely

anemia. Whether a child with convincing Peutz-Jeghers syndrome, who had colonic polyps, but none in the small intestine, has been observed is not certain,[12, 43] and the chance of malignant degeneration of these polyps is apparently not known. The writers have found no report of malignant change in such a polyp in a child. Although affected patients have pigment spots of the lips, face, hands and feet, the most diagnostic ones are those on the deep inner surface of the lips or elsewhere on the oral mucosa.[12, 43]

Carcinoid tumor also merits separate discussion. Probably all carcinoids should be regarded as having low-grade malignancy. They are found occasionally as incidental findings in the small intestine, usually ileum, of teen-agers, and rarely in younger children.[22] The interesting clinical and metabolic manifestations of the malignant carcinoid syndrome are well known. A child with full-blown malignant carcinoid syndrome has probably not been observed, but undoubtedly a rare patient will show early or partial manifestations. These include pulmonary vascular sclerosis with pulmonary hypertension, sclerotic changes of the right side of the heart, including the pulmonic and tricuspid valves, cutaneous telangiectasia, especially of the face, episodic flushing or cyanosis, hyperperistalsis with or without diarrhea, and bronchoconstriction.[34] Serotonin metabolites, especially 5-hydroxyindolacetic acid, are found in the urine, and the occurrence of a pellagra-like skin rash due to deviation of tryptophane into the abnormal metabolic pathway, and away from synthesis of nicotinamide coenzymes, has been suggested.[2] Apparently all carcinoids reported to cause this syndrome have arisen in the small intestine or colon, and none in the appendix. The metastases, apparently necessary before the mass of tumor tissue is large enough to produce serotonin intoxication, are classically in the liver, but may be in other sites, as the ovaries.[34]

Leiomyosarcoma of the small intestine is rare,[36, 42, 44] and by far the most common malignant tumor of the small intestine in childhood is *malignant lymphoma*, usually of the lower ileum. Obstructive symptoms usually precede systemic involvement,[16] so that initial treatment is commonly surgical. Radiation and chemotherapy are to be used as the resectability of the tumor, the degree of local spread or mesenteric involvement, and the presence of involvement of other organs, indicate. Fèvre and Huguenin[11] have described and the writers have observed patients in whom malignant lymphoma of the small intestine became manifest shortly after appendectomy, indicating the necessity of adequate local exploration when a grossly normal appendix is found in a child with symptoms suggesting appendicitis. Rarely, non-neoplastic lymphoid hyperplasia of the terminal ileum or ileocecal valve will produce obstructive symptoms ("cecal tonsil").

More than half of all duplications of the gastrointestinal tract involve

the small intestine (Tables 4 and 5). When the findings are those of obstruction, bleeding, and so on, distinction from neoplasms of the intestine is important, but when a mass is palpable, differentiation from other types of abdominal masses is more often necessary (Table 2). Gross[17] points out that mesenteric lymphatic cysts are typically flabby and thin-walled, and often dumbbell-shaped. Usually they can be dissected free of the adjacent intestine, whereas 93 per cent of Gross' 68 duplications were fused to the wall of the adjacent gut. Thus resection is generally necessary for duplication, except for those of the duodenum, where window-anastomosis is preferred to avoid injury to the ducts and blood vessels of the pancreas and liver.

Other tumors of the retroperitoneum, peritoneum and mesentery which must on occasion be differentiated from tumors of the gastrointestinal tract in children include the following (from Ackerman;[1] see also Table 2): retroperitoneum—liposarcoma, xanthogranuloma, myxoma, rhabdomyosarcoma; mesentery and omentum—*benign*—hemorrhagic cyst, lipoma, hemangioma, leiomyoma, neurofibroma, ganglioneuroma and desmoid tumor—*malignant*—malignant lymphoma, fibrosarcoma, liposarcoma, hemangiopericytoma and mesothelioma.

The rare occurrence of the several types of small intestinal tumors in a Meckel's diverticulum should be mentioned, as should the chance of development of gastric or pancreatic carcinoma in the ectopic tissues of a Meckel's diverticulum in later life.[16]

APPENDIX

Although polyp of the appendix has been reported, one was not observed in Gross'[17] series of 203 children with polyps of the large intestine. It is also doubtful whether carcinoma of the appendix has been recorded in a child. Malignant lymphoma often involves the appendix when it involves the terminal ileum, cecum or adjacent mesentery, and rarely only appendiceal involvement will be found on exploration. The symptoms are usually interpreted as those of appendicitis. The appendiceal carcinoids recorded in Table 1 represent approximately 1 in 500 surgically removed appendices in children up to 16 years of age. The rarity of malignant behavior of appendiceal carcinoids probably reflects, not a basic biologic difference, but early production of symptoms, perhaps because of local muscle spasm. As mentioned above, carcinoid primary in the appendix has apparently not been observed to cause the malignant carcinoid syndrome.

COLON AND RECTUM

Benign tumors of the large intestine which may occur in children include lipoma, lymphangioma, hemangioma, neurofibroma, leiomyoma

and ganglioneuroma.[11, 20, 48] Carcinoid tumor of the ileocecal valve has been reported in a child, but the writers have not found a description of one in the colon proper, nor have they discovered a record of lymphoid polyp (benign lymphoma)[19] of the rectum in a child. By far the most common "tumor" of the colon in children is polyp.[7, 10, 15, 17, 21, 25, 54] Painless bleeding is the typical clinical manifestation of those of the rectum, pain being more common with those situated more proximally. Gross[17] gives data on the site of colonic polyp in 203 cases (Tables 4, 5). In this large series only 5 patients had intussusception; the youngest patient was aged 15 months, and the peak incidence was at 4 to 5 years. Malignant change of a solitary polyp of the colon has apparently not been observed before puberty.[51] Villous adenoma of the colon has a high (at least 50 per cent) risk of malignant degeneration, but the writers have neither observed this tumor in a child nor found it reported.

Both Gross[17] and Swenson[51] recommend removal of rectal and sigmoid polyps with a wire snare and cautery through a sigmoidoscope or proctoscope. Higher polyps are best treated by laparotomy, incision of the bowel and excision of the polyp. When polyps are multiple (up to 15 polyps), several colostomies may be made and the polyps removed with snare and cautery through a sigmoidoscope. Although there is no real risk of malignancy in single colonic polyps, all removed should be examined microscopically because malignant lymphoma has been misdiagnosed as polyp on occasion.[11] As discussed on page 418, colonic polyps occur in the Peutz-Jeghers syndrome, and colonic polyposis has also been reported in a family with hereditary osteomatosis (leontiasis ossea).[39]

Hereditary multiple polyposis of the colon is transmitted as a mendelian dominant trait with incomplete penetrance.[41] Approximately one third of cases of multiple polyposis are "sporadic," but, because carcinoma invariably develops in patients with this disease who go untreated long enough,[19] the available relatives of any patient with the disease should be surveyed. The minimum number of polyps diagnostic of multiple polyposis is not known, but certainly any patient with more than 10 to 15 colonic polyps should be studied carefully. Diarrhea, often refractory to treatment, and bleeding, both usually appearing in the teens, are the typical clinical features of multiple polyposis. Because the number of polyps is usually too large (up to 400 have been described), the methods of treatment of polyps described above are not adequate. Swenson[51] recommends removing all the colon except 2 cm. of rectum, any polyps in which can be cleared via a proctoscope, and performing an ileorectal anastomosis. He states that the postoperative period of discomfort and diarrhea soon passes, and that patients treated by this method have done well up to seven years. Gross[17] apparently prefers to

leave a longer rectal segment, and to check the patients at intervals for development of new polyps. If the colon is not removed before carcinoma develops, it is important to realize that more than one carcinoma may be present.[7] Carcinoma has been observed as early as 12 years and often by 15 years.

Many studies of the frequency of *carcinoma of the colon in patients with ulcerative colitis* have been published.[6, 22, 27, 29, 59, 60] In Lagerkrantz's[29] collective review of 6890 cases carcinoma developed in 3 per cent (4.3 per cent in 115 patients whose disease began before the age of 20). Malignancy rarely develops in patients who have had ulcerative colitis less than 10 years, so that it is not commonly seen in childhood years (although Wilcox[60] reports one patient 11 years old and Mallory[35] one 13 years of age). The risk of approximately 5 per cent means that patients under medical regimens should be followed up closely. Cyto-

TABLE 6. *Distribution of Intestinal Polyps, 203 Cases*[17]

Rectum only	144	**Scattered in colon**	4
Sigmoid only	21	**Colon and rectum**	8
Descending colon only	8	**Ileum**	2
Transverse colon only	4	**Stomach, jejunum, ileum (had Peutz-Jeghers syndrome)**	1
Cecum only	1	**Multiple polyposis of colon**	10

General ratio: single polyp, two thirds of cases; 2–9 polyps, one third of cases.

logic abnormalities resembling those of malignant cells have been described in smears of the colonic mucosa of patients with ulcerative colitis,[3] but the degree of change appears to be related to the severity of an attack rather than to duration of illness, and the significance of these findings as to development of actual malignant tumors is not known.

Over 50 cases of *carcinoma of the colon* in children, unassociated with multiple polyposis or ulcerative colitis, have been reported.[4, 6, 21, 61] Mass, pain, vomiting and diarrhea are the usual clinical features, and bleeding is relatively rare. A 9-month-old girl with a large mucus carcinoma of the descending colon is described in the 1957 Cancer Seminar of the Penrose Cancer Hospital.[55] Despite their usually relatively good degree of microscopic differentiation, the prognosis of such tumors is poor, the longest reported survival in the series collected by Williams[61] being four years, and the longest in his own three patients, two years. Of 43 cases, 46 per cent were of the colloid or gelatinous type of carcinoma. (This type constitutes approximately 5 per cent of all carcinomas of the colon in adults.) Seventy per cent of the patients in this series were males.

Sarcomas of the colon also occur in children, the usual method of

production of symptoms being obstruction. The exact nature of some reported cases is not clear, but malignant lymphoma is certainly the most common type. The cecum and ascending colon are the usual sites, but primary lymphomas of the rectum do occur. The principles of diagnosis and treatment do not differ from those for malignant lymphomas of the small intestine or appendix, but surgical removal is, if anything, less often curative.

PANCREAS

The pancreas is often partially surrounded or invaded by malignant lymphoma, Hodgkin's disease or neuroblastoma, but symptoms of pancreatic insufficiency (diabetes mellitus or pancreatic achylia) are rare. The writers have seen an infant with obstructive jaundice due to benign *hemangioendothelioma* of the head of the pancreas. Primary malignant tumors of the pancreas in childhood have been reported,[11, 51] but the exact cell type of most described cases is not clear. True *cysts of the pancreas* are also rare, and usually cause symptoms during the first year. When in the tail, they tend to become larger before causing symptoms, those of the head producing duodenal or hepatic portal compression early. Mass is the usual clinical manifestation, but abdominal pain, "dyspepsia," vomiting, icterus and diarrhea (pancreatic achylia) may occur. Differential diagnosis includes the other types of abdominal cysts and tumors listed in Tables 2, 4 and 5. Complications include rupture of the cyst, infection, and torsion of a pedunculated cyst. Surgical removal is the preferred treatment, but marsupialization or partial resection with drainage may be necessary, particularly for those involving the head of the pancreas. True pancreatic cysts usually contain clear viscous fluid, and *pseudocysts* darker brownish liquid. Polycystic disease of the pancreas also occurs, but the writers have not found a report of this condition's causing symptoms in a child. Pseudocysts probably usually result from injury, pancreatitis being rare in children.

Islet cell tumors are rare. Talbot et al.[53] had not observed an islet cell tumor producing hyperglycemia in a child under 16 years of age at the Massachusetts General Hospital or the Boston Children's Medical Center. In their detailed review of 398 islet cell tumors Howard et al.[23] found 14 recorded cases of benign islet cell tumor in children up to 15 years of age, but in 4 of these a tumor was never actually demonstrated by operation or autopsy. Howard et al. found reports of suspiciously malignant tumors in 1 infant and in three 18-year-old boys, and a report of carcinoma in an 18-year-old girl who died with liver metastases. In the material of this survey 12.6 per cent of 340 patients had more than 1 tumor. Whether all such patients in the younger

age group have the *familial syndrome of adenomas of the pituitary, parathyroid glands and pancreatic islets*[56] is not certain, but this possibility should be considered. The association of pancreatic islet cell tumor and peptic ulceration (ulcerogenic tumor of the pancreas)[9] should also be mentioned, although the writers have not discovered a report of this association in a child.

Islet cell tumor is an infrequent cause of hypoglycemia in children. Gross[17] found no example in six children treated by subtotal pancreatectomy for hypoglycemia. Whether such tumors can be differentiated from other causes of hypoglycemia by function tests is not clear, but hypoglycemia caused by islet cell tumor may respond to ACTH.[45] Alloxan has not been of value in the treatment of islet cell tumors, and surgery is recommended.[52] In the series of Howard et al.[23] 9 of 398 islet cell tumors occurred outside the pancreas, 4 near the tail, 2 in the wall of the duodenum, 2 near the head, and 1 in the omentum.

Ectopic pancreatic tissue in the stomach, small intestine and Meckel's diverticulum has been discussed above. Depending on the site, pain, bleeding, obstruction and intussusception may occur, and these nodules may be sites of pancreatic carcinoma in later life.

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BENIGN AND MALIGNANT TUMORS OF THE LIVER

ROBERT S. CLELAND, M.D.

Although the liver is frequently involved by metastatic neoplasm, it is rarely the site of a primary tumor in the pediatric age period. The primary tumors which do occur are commonly malignant and rapidly fatal. It is understandable, therefore, that the discovery of a liver tumor is frequently considered indicative of a hopeless prognosis. Recently Edmondson[6] emphasized that this is not necessarily true. He lists a number of tumors and tumor-like lesions which are essentially benign. Such cases are rare, and may at times cause death. It is important to be aware, however, that they do exist, that they may be cured, and that they may or may not need treatment.

The records of the Children's Hospital of Los Angeles contain at least one example of each of the following: hemangioma, infantile hemangioendothelioma, hamartoma, nonparasitic cyst and focal nodular hyperplasia. In almost every instance the lesion was completely new and unfamiliar to the examiner at the time of its discovery. It seems worth while, therefore, to review the characteristic features of these lesions, and the problems of diagnosis, management and prognostication they have presented in this institution. Primary malignant tumors and a few illustrative diagnostic problems are included to clarify certain features of differential diagnosis.

During the 57 years prior to July, 1958, 71 patients were considered to have a tumor or cyst of the liver at the time of discharge from the hospital. The clinical records of these patients were reviewed, and when it seemed possible that the lesion was a primary tumor, available anatomic material was examined. In 28 cases one or more histologic sections indicated a primary lesion of the liver. In one case (case 4) no

From the Children's Hospital of Los Angeles, and the Department of Pathology, University of Southern California School of Medicine, Los Angeles.

TABLE 7. *Primary Tumors and Tumor-like Lesions of the Liver*

CASE	AGE	SEX	DIAGNOSIS	COMPLAINT	DIAGNOSIS AND TREATMENT	OUTCOME	COMMENT
1.	12½ years	M	Liver cell carcinoma	No symptoms Mass discovered by mother 1 week, by patient 1 month	Exploration 6 months later, x-ray therapy	Died 1 year later	Biopsy diagnosis, adenomatosis Autopsy, metastasis present
2.	10½ years	F	Liver cell carcinoma	No symptoms Mass discovered by mother 1 month, by patient 8–12 months	Exploration Resection	Alive with no evidence of metastasis 8 months later	Localized lesion, left lobe
3.	8 years	M	Liver cell carcinoma	——	——	Tumor discovered at autopsy, metastasis present	De Toni-Fanconi syndrome Hepatomegaly, 6 years Cirrhosis proved by biopsy 5½ years
4.	6 years	M	Liver cell carcinoma	Pain, right knee, and limp, 2 weeks	Biopsy of knee lesion	Died at home 2–3 months later	Biopsy, liver cell carcinoma No autopsy
5.	1½ years	F	Liver cell carcinoma	Febrile episodes, 2 months Vomiting, 1 month	Exploration and biopsy	Discharged in critical condition, no follow-up	Biopsy, carcinoma X-ray, calcification of liver
6.	1 year	M	Hepatic mixed tumor	Palpable mass, 1 month	Exploration and biopsy	Died in 1 month	Biopsy diagnosed neuroblastoma Autopsy, metastases present
7.	9 months	F	Liver cell carcinoma	Abdominal enlargement, 4 months Vomiting, 1 month	Exploration and biopsy	Died 3 weeks later	Autopsy, no metastases
8. *† ...	6 months	F	Hepatic mixed tumor	Abdominal swelling and pallor, 2 months	Exploration	Died 10 days later	Liver soft, spongy, hyperemic Autopsy, no metastases
9.	6 months	M	Undifferentiated sarcoma	Abdominal swelling and irritability, 3 days	Exploration	Died 3 weeks later	Diffusely enlarged, soft liver at operation, thought to be hepatitis Autopsy, metastases present
10.	6 months	M	Hepatic mixed tumor	Abdominal enlargement	Exploration and biopsy	Died 2 weeks later	No autopsy
11.	6 months	M	Hepatic mixed tumor	Vomiting, 2 weeks Abdominal swelling, 1 week	Exploration and biopsy, x-ray therapy	Died 3½ months later	Liver smooth, no tumor discovered at operation Storage disease ? type Autopsy, no metastases
12.	4½ months	M	Hemangioma, 6 cm.	——	——	——	Incidental finding at autopsy
13.	4½ months	M	Hemangioma, 6 cm.	——	——	——	Incidental finding at autopsy

14.	15 years	M	Hemangioma, 3 cm.	——	——	——	Incidental finding at autopsy
15.	10½ weeks	F	? hemangioma Possible massive hematoma	No symptoms Abdominal mass	Exploration	Alive and well	No biopsy Massive hemorrhage at operation
16. *†‡	6 months	F	Infantile hemangioendothelioma	Pallor, 1 month Abdominal mass, 1 week	Exploration and biopsy	Alive and well 10 years later	Diagnosis of malignant tumor made at operation Diffusely nodular liver
17.‡	10 days	F	Infantile hemangioendothelioma	Cyanosis since birth Vomiting, syncope	——	Died 5 days later	Large heart by X-ray. Localized lesion encroaching on biliary tree at autopsy
18.‡	3 months	M	Infantile hemangioendothelioma	Jaundice Abdominal enlargement	Repair of evisceration	Died 1 day after operation	Diagnosis of malignant tumor made after operation elsewhere. Heart enlarged by x-ray. Autopsy
19.	20 months	M	Mesenchymal hamartoma	Abdominal enlargement and pain, 2 months	Exploration and rupture of cysts	Alive and well, with no enlargement of liver, 1 year later	——
20.§	5½ months	F	Nonparasitic cyst	Abdominal enlargement, 3 months	Excision of cyst	Alive and well	——
21.*§	7 years	F	Nonparasitic cyst	Abdominal enlargement, pain, 4 weeks	Drainage of cyst	Alive and well 4 years later	——
22.§	2 years	M	Nonparasitic cyst	Protruding abdomen, 9 months Enuresis, edema	Excision of cyst	Alive and well	——
23.§	11 years	M	Nonparasitic cyst	Abdominal enlargement, 10 months	Marsupialization	Alive and well	Cyst arose in accessory spleen
24.§	3 days	F	Nonparasitic cyst	——	——	——	Incidental finding at autopsy
25.§	4½ years	M	Nonparasitic cyst	——	——	——	Incidental finding at autopsy
26.§	1 day	M	Nonparasitic cyst	——	——	——	Incidental finding at autopsy
27.	6½ years	F	Focal nodular hyperplasia	No symptoms Mass, 5½ years	Excision	Died 2 days after operation from bleeding diathesis	Autopsy
28.	8 months	F	Focal nodular hyperplasia	No symptoms Mass, 1 day	Exploration and biopsy	Alive and well 8 years later	——
29.	3½ years	M	Undiagnosed	Abdominal pain and fever, 4 days	Exploration and biopsy	Alive and well, with mental retardation, 5 years later	——

* This case mentioned in Edmondson.[6]
† This case mentioned in Edmondson.[7]
‡ Reported in Crocker and Cleland.[4]
§ Reported in Desser and Smith.[5]

material was available, but the fact that several competent pathologists had unhesitatingly agreed to a diagnosis of liver cell carcinoma was accepted as proof of the nature of this lesion. Thirty-five of the remaining cases were metastatic tumors, 4 were examples of erroneous diagnoses, 1 was a hematoma of the liver, 1 a cystic dilatation of the extrahepatic bile ducts, and 1 a carcinoma of the liver which was excluded because the age of the patient (19 years) precludes its consideration as a tumor of childhood. The 29 cases accepted as primary tumors are summarized in Table 7. Lesions are classified as suggested by Edmondson,[7] and distribution of lesions indicated in Table 8.

TABLE 8. *Distribution of Primary Tumors of the Liver in Children under 16 Years of Age*

	THIS SERIES	LITERATURE
Malignant		
Carcinoma	6	(Combined)
Hepatic mixed tumor	4	At least 101*
Mesenchyma	0	At least 2†
Sarcoma	1	At least 2†
	11	At least 109
Benign		
Adenoma	0	2†
Adrenal rest tumor	0	2†
Hemangioma	3 or 4(?)	6†
Infantile hemangioendothelioma	3	At least 24‡
Mesenchymal hamartoma	1	11†
Nonparasitic cyst	7	At least 28†
Focal nodular hyperplasia	2	At least 8†
Unclassified	1	0
Total	17 or 18(?)	At least 81
Total malignant and benign	28 or 29(?)	At least 190

* References 1, 2, 13.
† References 6, 7.
‡ References 10, 14.

METASTATIC TUMORS

No effort was made to determine the exact incidence of metastasis to the liver from other sites. The 35 cases discovered incidentally in the course of the study include 11 cases of Wilms' tumor and 13 cases of neuroblastoma. The primary tumor in the remaining patients frequently occurred in the pelvis or the retroperitoneal space. The extrahepatic origin of the primary tumor was determined before operation in most cases.

DIAGNOSTIC PROBLEMS

Four patients were erroneously considered to have hepatic tumors until postmortem examination revealed the correct diagnosis. In one the diagnosis of tumor was based on clinical evidence, and a granulomatous disease of undetermined cause was found at necropsy. The other three illustrate the problems which beset the pathologist in the interpretation of liver biopsies. Andersen[1] called attention to the possibility of confusing extensive bile duct proliferation with carcinoma of the bile ducts. One of the cases under consideration is an example of this error. A biopsy several days before death revealed distortion of architecture and extreme bile duct proliferation suggesting carcinoma. At necropsy no tumor was found. The liver was collapsed with extensive necrosis and fibrosis. In a second case, seen more than 10 years ago, extrahepatic biliary atresia was discovered at laparotomy. Bizarre giant cells were present in a biopsy of the liver and were interpreted as evidence of carcinoma. No neoplasm was discovered at autopsy. It is now widely recognized that this alteration may be found in some cases of biliary atresia as well as in other disorders of the liver in infancy.[3] A similar misinterpretation probably occurred in case 5 of this series. Areas of carcinoma are present in the biopsy, but there is also extensive giant cell alteration. The diagnosis of carcinoma was correctly made, but the description indicates that the giant cells as well as the tumor cells were considered malignant. Case 1 of this series and a case seen several years ago illustrate a common pitfall in the interpretation of surgical specimens. The earlier patient had a multinodular liver at laparotomy, and a histologic diagnosis of carcinoma was made. At death the liver was cirrhotic, but free of tumor. On the other hand, biopsy in case 1 was interpreted as adenomatosis, but death resulted from a well differentiated liver cell carcinoma. It is obvious that extreme caution must be used in the interpretation of adenoma-like nodules of the liver.[7] If this study had included all cases in which hepatic tumor was considered in the initial diagnosis, many other instances of confusion would undoubtedly have been found.

MALIGNANT TUMORS

Eleven malignant tumors are included in the series. Six occurred in males and five in females. One patient (case 7) was Oriental, the remainder Caucasian. The age range was from 6 weeks to 12½ years. Six patients were less than 1 year old; 4 were between 6 and 12½ years. Autopsy was performed in seven fatal cases. The diagnosis was made on biopsy alone in three. One patient is still alive and the resected tumor available for study.

Two patients (cases 4 and 11) diagnosed by biopsy are known to have died at home after discharge from the hospital. Biopsy from case 11 showed a typical hepatic mixed tumor. Biopsy of metastasis to bone in case 4 was not available for review. It had been identified as liver cell carcinoma by several competent pathologists. The third patient (case 5, Fig. 41) was in critical condition when taken home by her parents, but we have been unable to verify the outcome. It seems probable that survival was brief, since an appointment to return for removal of sutures was not kept. The liver biopsy in this case is most interesting. At one edge there is a small fragment of well differentiated liver cell carcinoma. The remaining liver parenchyma is distorted and

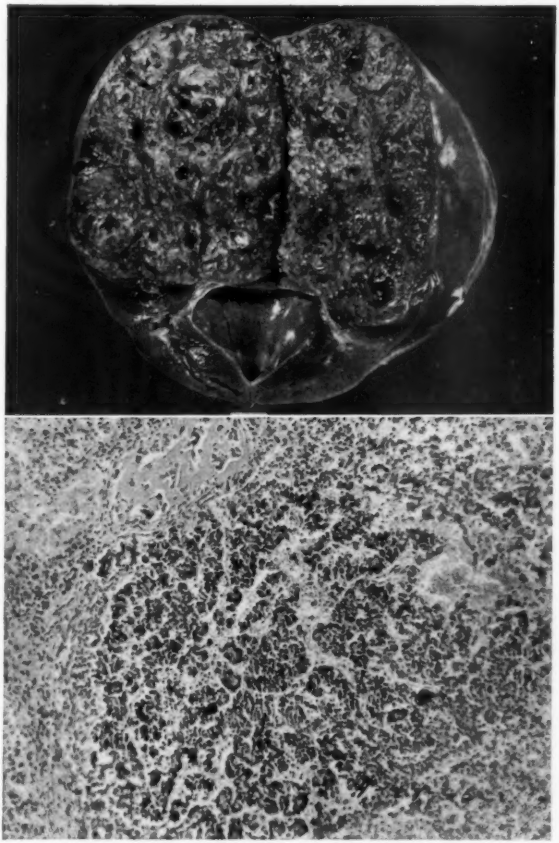
Fig. 36. Case 6. Hepatic mixed tumor. Hard nodular liver with areas of osteoid and calcification

fibrotic with rather extensive swelling and at times giant cell transformation of cells. It is probable that this is a liver cell carcinoma, but the presence of extensive calcification on roentgen examination suggests the possibility that other areas of the liver might have contained mixed tumor.

Necropsy was performed in 2 patients between 6 and 12½ years of age (cases 1 and 3), and in 5 patients less than 1 year old (cases 6, 7, 8, 9, 11). The tumors of the older patients were readily identified as liver cell carcinoma, although the degree of differentiation varied. In none was the tumor as cellular or as difficult to classify as in the infants. As has been observed by others,[1, 2, 6, 15] the tumors of the younger patients were cellular, poorly differentiated, and difficult to classify. These tumors were composed of small cells with scanty cytoplasm. In places they formed definite liver cords, and in places the arrangement suggested bile ducts. Initial examination frequently suggested rosette formation, but more careful observation revealed that this appearance was produced by poorly differentiated cells arranged about a central lumen. The resemblance to neuroblastoma was superficial, but in one

case led to the biopsy diagnosis of metastatic tumor. In case 7 no osteoid was present, and there was no alteration of the scanty stroma. This case is considered a liver cell carcinoma. In cases 6, 8, 10 and 11 large amounts of osteoid were present, and malignant change was observed in the stroma at times. These tumors are classed as hepatic mixed tumors. In case 9 (Fig. 40) the cells were poorly differentiated, but showed evidence of fiber formation in large portions of the lesion. No osteoid was present. This tumor was classified as an undifferentiated

A



B

Fig. 37. Case 8. Hepatic mixed tumor. A, Diffuse, soft, hyperemic and cystic. B, Note osteoid in upper portion of picture. Poorly differentiated tumor. Cells are small. Stroma scanty. Liver cord pattern evident. In places rosette-like pattern is seen. H & E. × 175.

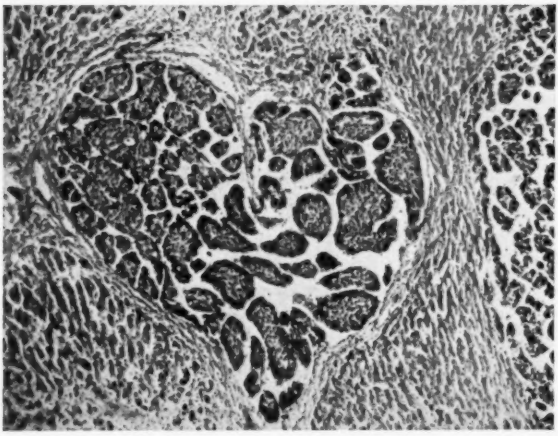


Fig. 38. Case 3. Liver cell carcinoma in older child. Tumor is well differentiated. H & E. × 96.

Fig. 39. Case 2. Localized liver cell carcinoma. Tumor was resected. Patient alive 8 months later.

sarcoma. Metastases were present at autopsy in the sarcoma, one hepatic mixed tumor, and two liver cell carcinomas.

The primary tumor in the older children produced no symptoms and developed insidiously. In one the tumor was an unexpected finding at necropsy. The first symptom of another was pain from a metastasis in bone. An abdominal mass was discovered by the mother of two others. Both children had been aware of the mass for several months, but no other symptoms had occurred. The development of the lesion was usually more apparent in infancy. Rapid enlargement of the abdomen

was the most frequent sign. Restlessness and irritability were common. Vomiting occurred commonly and pallor occasionally.

The liver was invariably enlarged. In the older patients it was usually stony hard and confined to the upper part of the abdomen. In one it was nodular, and in another a discrete mass could be outlined. The findings were similar in some of the infants, but more often massive,

Fig. 40. Case 9. Undifferentiated sarcoma. Immature cells. Fibrous pattern. H & E. × 96.

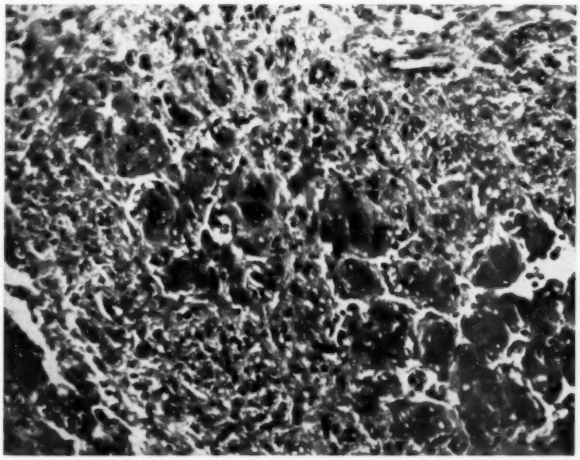


Fig. 41. Case 5. Cirrhosis and giant cell alteration. In other portions of the tissue liver cell carcinoma was present. At least 2 other reported carcinomas were associated with this lesion.

diffuse enlargement was noted, with extension below the umbilicus and into the pelvis. The usual consistency was firmness rather than hardness, and the surface of the liver was more often smooth than nodular.

Nine patients were subjected to laparotomy. In most the liver was described as nodular, and frequently a larger mass was evident, representing the apparent site of origin. One liver was smooth and apparently free of tumor. Another was diffusely enlarged, soft, spongy and extremely hyperemic. Both were hepatic mixed tumors. The sarcoma caused diffuse enlargement with a gray, friable surface. It was considered inflammatory before examination of the histologic sections.

One liver cell carcinoma (case 2, Fig. 39) was localized to the left lobe without evidence of extension. Lobectomy was performed, and the child has survived eight months without evidence of metastasis. The period of observation is too short to determine the ultimate effect of the operation,[8] but the result is encouraging at present.

In general, the prognosis of these tumors is poor.[2] The sarcoma produced the most fulminating disease, causing death within three weeks of the first symptoms. The longest survival was one year. The tumor of this patient was sufficiently well differentiated to be considered an adenoma. Roentgen therapy was given in two patients and chemotherapy in one without apparent effect.

Neoplasm occurred in a previously diseased liver in cases 3, 11 and possibly case 5. Case 11 suffered a storage disease, the exact nature of which is undetermined. Case 3 was a well documented example of the de Toni-Fanconi syndrome in which cirrhosis was proved by biopsy five years before death. In case 5 lack of autopsy confirmation prevents definite conclusions. It is probable that this represents another instance of carcinoma arising as a sequel to giant cell hepatitis.

BENIGN LESIONS

Hemangioma

Hemangioma of the liver is benign, usually solitary and asymptomatic. It is usually an incidental finding at necropsy. The three definite cases in our series were encountered in this way. They were localized but poorly circumscribed spongy lesions, 1.5 to 6 cm. in diameter. In an older boy the histologic examination revealed large channels lined by a single layer of endothelium. Walls were composed of dense connective tissue. In the two infants many of the channels were smaller, and the walls frequently contained cords of hepatic cells. The appearance suggested permeation of the hepatic parenchyma by a growing lesion, although the active proliferation seen in the infantile hemangioendothelioma was not evident.

In three recorded cases hemangioma caused death by spontaneous

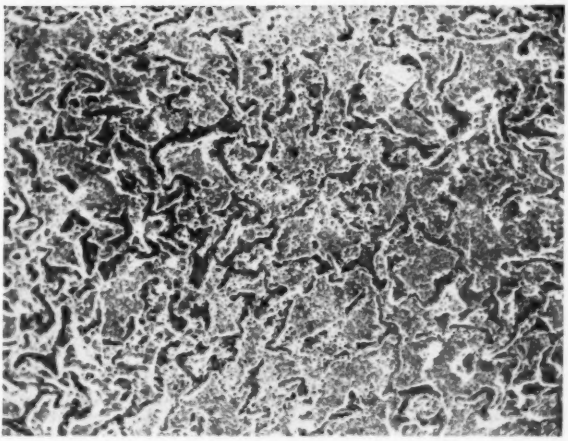


Fig. 42. Case 13. Cavernous hemangioma in an infant. Vascular spaces lined by a single layer of flat endothelium. Liver cells present in walls. H & E. × 96.

rupture and hemorrhage.[7] It is possible that case 15 is an example of this complication.

The patient underwent exploratory laparotomy at age 10½ weeks because of an abdominal mass causing no symptoms. The liver was diffusely enlarged and smooth. As the under surface was gently palpated, a sudden and massive hemorrhage occurred, and the liver rapidly decreased in size. Bleeding was controlled with great difficulty. The critical situation made biopsy inadvisable, and it is uncertain whether the lesion was a hemangioma or a massive hematoma. Six years later the child is well with no evidence of recurrence.

Infantile Hemangioendothelioma

Infantile hemangioendothelioma of the liver occurs almost exclusively in the first six months of life. It may occur as a solitary lesion, or it may cause extensive nodularity of the liver suggesting malignancy. Histologically, it is reminiscent of hemangioma of the skin in young infants. Vascular channels lined by one or several layers of plump endothelial cells show evidence of active proliferation at the periphery. Central areas appear more mature and may contain thrombi. Clinically, the tumor usually causes abdominal enlargement and symptoms of pressure on other structures. A number of reports [4, 11, 16] indicate that infantile hemangioendothelioma may mimic congenital heart disease and cause cardiac failure as a result of its action as an arteriovenous shunt. It may cause death because of local pressure effects or as a result of heart failure. We feel that the tumor is basically benign and that it may undergo spontaneous regression as does the hemangioma of the skin.

Surgical excision is the treatment of choice, but irradiation may be effective if resection is impossible.

The three cases in this series have previously been reported in detail.[4] Two patients died in early infancy, but one is alive and well 10 years later, although at operation a diagnosis was made of inoperable carcinoma. During the first two weeks after operation the hepatic nodules continued to grow larger. During the following month no

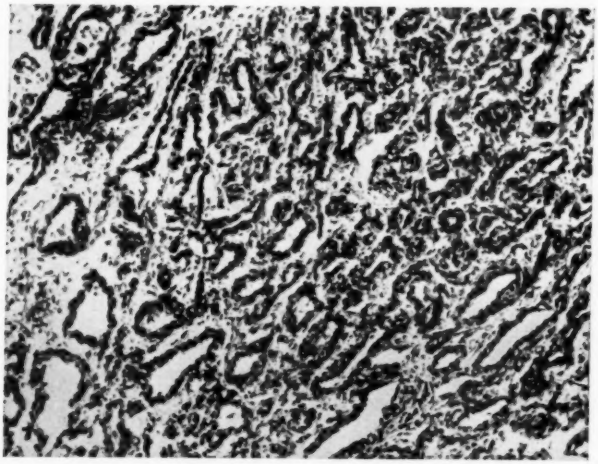


Fig. 43. Case 16. Infantile hemangioendothelioma. Note multilayered endothelial lining. H & E. × 192.

change was noted; thereafter there was gradual regression. It is our belief that the lesion may regress spontaneously if a patient can be kept alive during the period of its active growth.

Mesenchymal Hamartoma

Several of the lesions under consideration are considered hamartomas by many pathologists.[7] We feel, however, that this designation should be reserved for the specific cystic lesion illustrated by case 19. The exact nature of the lesion is not clear, but its gross and histologic appearance is characteristic.

Our patient was a 20-month-old boy hospitalized because of abdominal enlargement. A cystic mass was palpated in the right upper quadrant. At operation most of the right lobe of the liver was replaced by a multicystic mass which resembled a cystic hygroma. Incision of the cyst yielded clear watery fluid. An attempt to resect the involved area was deemed inadvisable. Accordingly, the cysts were drained individually until the lesion was completely collapsed. When last seen 14 months later, the patient was clinically well, and his liver was not palpable.

These lesions may be fixed or pedunculated.[6] They are composed of multiple cysts up to 2 to 3 cm. in diameter. Histologically, they contain large amounts of connective tissue which may be mature or mesenchymal in appearance. A peculiar honeycomb appearance is produced in places by large fluid-filled spaces separated by thin strands of tissue. Lining cells suggest mesothelium. Foci of hemopoiesis are occasionally evident. Presumably this is a benign mesenchymal tumor. Its growth can be attributed to accumulation of fluid in the cysts rather than to active proliferation. Operative removal of the tumor is desirable, but simple

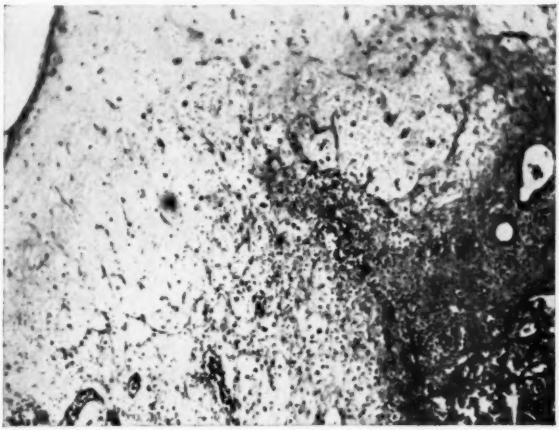


Fig. 44. Case 19. Mesenchymal hamartoma. Areas of fibrosis with bile duct proliferation at one edge. Typical fluid-filled spaces on the other. H & E. × 96.

incision and drainage of the cysts may be preferable when resection would be hazardous.

Nonparasitic Cysts

The seven cases of nonparasitic cysts encountered in this hospital through April, 1956, were previously reported by Desser and Smith.[5] Since then no examples have been seen.

In 3 patients (cases 24 through 26) the cyst was an incidental finding at autopsy; in the others the presenting complaint was upper abdominal enlargement. The cystic nature of the lesion was detected before operation in three of the patients. A variety of surgical procedures were used, and all patients have done well.

Only a small bit of tissue was available in case 21 and consists of dense fibrous tissue in which there is extensive hemosiderin deposition compatible with the history of recent trauma. In cases 20 and 22 the

Fig. 45. Case 22. Nonparasitic cyst. Note multilocular appearance. Most are unilocular.

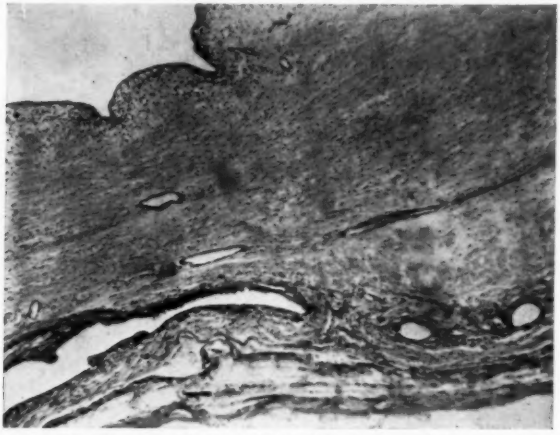


Fig. 46. Case 20. Nonparasitic cyst. Note bile duct epithelium lining cyst, dense connective tissue wall, and ductlike structures in wall. These are also lined by bile duct epithelium.

cyst was lined by biliary duct epithelium. The wall was dense and fibrous. In it small and dilated ductlike structures were evident. The picture is highly reminiscent of that seen in polycystic disease of the liver. Review of the tissue in case 23 revealed splenic instead of hepatic tissue in the wall. Since occurrence of the cyst in the left lobe of the liver has been well established, it is probable that this represents development of a cyst in an accessory spleen adherent to the liver. Material from two newborn infants was examined. In both there were

multiple, subcapsular cysts lined by mesothelium. It is probable that some of these cysts represent a localized abnormality of development similar to that seen in polycystic disease of the liver. The mesothelial-lined lesions are apparently inclusion cysts. They are benign, though capable of producing symptoms by pressure on adjacent structures. Since at times death from shock[5] has followed rapid evacuation of such cysts, they must be considered potentially lethal. Adequate surgical drainage should result in complete cure.

Focal Nodular Hyperplasia

Focal nodular hyperplasia is another lesion whose nature is not clear. Grossly, its appearance is characteristic and suggests a localized area of cirrhosis. The parenchyma is firmly nodular, and traversed by numerous fibrous bands which tend to radiate from a central stellate mass of connective tissue. The lesion may be pedunculated or may lie in the hepatic parenchyma. Histologically, a similar central mass of fibrous tissue is permeated by small bile ducts and scattered lymphocytes. This is surrounded by normal-appearing hepatic cells arranged radially.

A large abdominal mass was found in the right upper quadrant of a 6½-year-old girl (case 27) during a routine examination at school. Apparently the mass had been present since the first year of life, at which time the mother was told that the child had an accessory lobe of the liver. It had caused no symptoms. At laparotomy a large, pear-shaped, finely nodular mass was identified, with a central stellate depression on the broad, unattached end. The lesion was attached at the opposite end to both the left and right lobes of the liver and had caused some distortion of the biliary tree. Resection was readily accomplished, an unexplained bleeding diathesis occurred, and the patient expired 2 days later.

A second patient (case 28) entered because of the discovery of an abdominal mass. A finely nodular, firm mass of tissue, somewhat paler than normal liver, was discovered in the right lobe. The lesion was considered inoperable, and the girl is alive and well 8 years later. The histologic picture in this case is that of focal nodular hyperplasia.

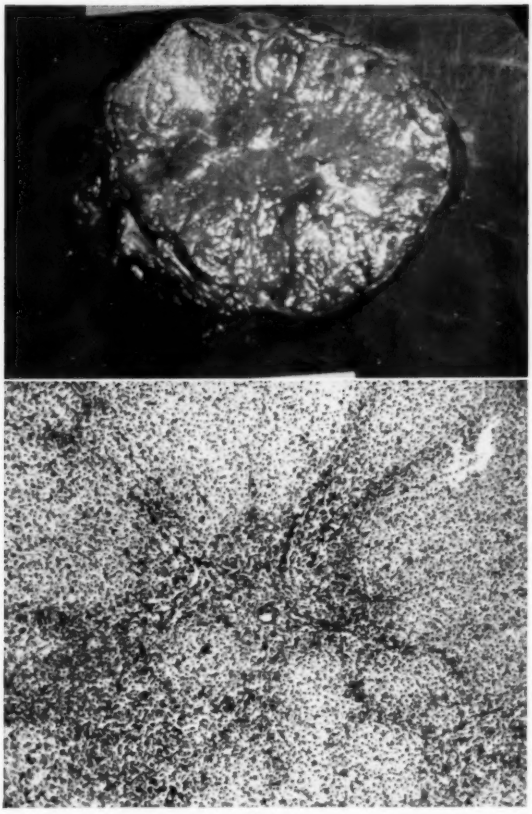
Undiagnosed

Case 29 remains unclassified.

A boy entered Children's Hospital at the age of 3½ years with the complaint of abdominal pain for 4 days and discovery of an abdominal mass the day of entry. The liver was enlarged. A mass 5 by 6 cm., moving with respiration, was present in the left upper quadrant. At operation an 8-cm. firm mass was present in the left lobe of the liver and a smaller, similar mass in the right lobe. Biopsy was taken and no attempt made to resect the lesions. Five years later the mass was still present. The boy was physically well, but severely retarded mentally.

Histologically, the outstanding feature of this lesion is the presence of large irregular masses of dense, acellular fibrous tissue. Within it there are numerous small spaces. Some of these are proliferating small bile ducts, others small blood vessels, and still others, lined by plump,

A



B

Fig. 47. Case 27. Focal nodular hyperplasia. *A*, This was a pedunculated pear-shaped mass encroaching on bile ducts. Note the nodularity of the surface and the central depressed fibrous area with radiation of fibrous bands through parenchyma. *B*, There is a central fibrous area in which proliferating bile ducts and lymphocytes are numerous. Fibrous bands separate lobules of normal liver cells.

elongate cells, resemble some of the spaces seen in the hamartoma. Masses of fibrous tissue join and permeate the tissue, cutting off irregular lobules of liver cells. The centers of the fibrous masses appear inactive. At the periphery the tissue appears more cellular and proliferative. At times many lymphocytes are present. The liver cells are swollen and finely vacuolated, suggesting the presence of glycogen or lipid. Many cells are multinucleated. Unfortunately, material was not available for special staining.

The nature of the process is not clear. Certain features are suggestive of focal nodular hyperplasia, others of cystic disease, and still others of hamartoma. The alteration of liver cells suggests a storage disease or an active process of hepatocellular damage. If the mental retardation is related, either a hamartomatous process, as seen in tuberous sclerosis, or a storage disease would seem most probable.

DISCUSSION

The figures in Table 8 were derived from major reviews and give an approximation of the relative frequency of various tumors and tumor-like lesions of the liver. In the reviews of Steiner[15] and of Bigelow and Wright[2] there are 95 cases of primary carcinoma of the liver. They make no distinction between carcinoma and hepatic mixed tumor. These lesions are therefore combined in the table. To their cases are added five cases described by Andersen[1] and the case of Roth and Duncan.[9]

In the reported cases of primary carcinoma of the liver in children[2, 15] there was a preponderance of males (2.3:1). The majority (55 of 95 cases) were children less than two years of age. Enlargement of the abdomen or discovery of an abdominal mass was the most common manifestation of the tumor. Dull pain in the epigastrium occurred frequently, and vomiting, anoxia and weight loss occasionally. Jaundice and ascites were rare. When jaundice did occur, it was due to obstruction rather than to hepatocellular injury. The onset was often acute, but more frequently insidious. The tumor was sometimes solitary, sometimes multinodular. It was usually soft, cellular and poorly differentiated. No recoveries were noted, and survival from onset of symptoms averaged four months.

Our experience was similar, although preponderance of males was not evident, and pain was an uncommon finding. The previous authors[2, 15] did not relate the type of onset to the age of the patient or the maturity of the tumor. In our experience a slow, insidious onset occurred in older patients whose tumors were usually well differentiated. In infants clinical signs were more acute, and the tumors poorly differentiated.

The association of previous hepatic disease and carcinoma of the liver is considered rare in children, although frequently observed in adults.[15] In one of our cases cirrhosis preceded the appearance of a malignant tumor by several years. In another it is highly probable that giant cell change and cirrhosis were present before the tumor. Bigelow and Wright[2] list four cases of cirrhosis in the 18 cases of carcinoma they reviewed subsequent to Steiner's[15] report. Andersen[1] reports one case of biliary atresia in her series, and Roth and Duncan[13] describe a primary carcinoma associated with giant cell hepatitis. In at least

three of these cases this bizarre alteration of liver cells was present (Fig. 41). Further investigation of the relationship of this reaction to neoplasia seems indicated.

The possible relationship between neoplasia and metabolic disorders offers another field for study. A patient of Andersen's,[1] not included in her reported cases, had glycogen storage disease, and in our patient with cirrhosis the de Toni-Fanconi syndrome was definitely established. The coincident occurrence of such rare lesions and the rare primary carcinoma of the liver suggests a more than casual association. Several reported cases and one of our cases seem related and may also represent a primary disorder of metabolism. Edmondson[7] describes extreme demineralization of the skeleton in one patient. Hansen et al.[9] found similar demineralization, hyperlipemia and widespread involvement of the tissues by foam cells. Wood[17] considered his patient an example of Niemann-Pick disease. In our own patient, biopsy revealed excessive glycogen in the liver, and at necropsy foam cells containing both glycogen and lipid suggested a metabolic disorder related to Niemann-Pick disease. The case of Roberts and Sullivan[12] was similar, but more complex. During a period of enlargement of the liver, extensive demineralization occurred, and a liver biopsy showed large amounts of glycogen, eventually considered within normal limits. Temporary improvement occurred with decrease in the size of the liver and beginning restoration of the skeletal calcification. With worsening of the patient the liver became nodular, and biopsy revealed carcinoma. In addition, many foam cells suggestive of Gaucher's cells were observed. It is probable that these five cases are examples of the same disorder. Whether it results from disturbed hepatic function or whether it represents an unusual primary disorder of metabolism resulting in hepatic injury and malignant degeneration is not decided. The cases of metabolic disturbance mentioned above suggest possible validity of the latter explanation.

Benign lesions of the liver are only occasionally of sufficient clinical importance to justify discussion in the literature. It is probable, therefore, that the incidence of these lesions in our series more clearly reflects their actual frequency than do the reported cases (Table 8). From Edmondson's reviews,[6, 7] it is apparent that, although these lesions are benign, they may at times cause symptoms and even death. Focal nodular hyperplasia may produce pain, but usually causes no symptoms. Mesenchymal hamartoma, nonparasitic cyst and hemangioendothelioma may enlarge and produce gastrointestinal or respiratory symptoms by pressure on adjacent structures. Hemangioendothelioma may produce cardiac failure and is frequently lethal. The hamartoma and the nonparasitic cyst, if pedunculated, may undergo torsion. Hemorrhage into the cyst, rupture or inflammation are other possible complications.

Hemangioma is usually asymptomatic, but in the newborn period may cause massive hemorrhage and death. Infantile hemangioendothelioma occurs in patients under six months of age. This lesion, nonparasitic cyst and hemangioma are the benign lesions most frequently discovered in the newborn period. Hamartoma is encountered only in patients under 20 months, while nonparasitic cyst may become manifest after 2 years. No other specific age incidence is noted. The most common manifestation of these lesions, as of malignant tumors, is enlargement of the abdomen or the presence of an abdominal mass.

CONCLUSIONS

The detection of an abdominal mass or enlargement of the abdomen in infancy or chilhood is frequently the prelude to discovery of an abdominal tumor. Such tumors are most frequently Wilms' tumors or neuroblastomas. Rarely, a primary tumor of the liver may be present. Discovery of such a tumor often causes confusion as to the nature of the lesion and its proper management. It is obviously important that every effort be made to determine before operation the lesion or lesions most likely to be encountered. Usually an exact diagnosis cannot be made preoperatively, but several observations may assist in evaluating probabilities. Most frequently the liver is involved by metastasis from a primary tumor elsewhere. Appropriate diagnostic measures should be undertaken to establish the presence or absence of such an extrahepatic tumor. Jaundice accompanies hepatic tumors infrequently, and its presence should suggest either diffuse hepatic disease such as hepatitis, or an extrahepatic or intrahepatic obstructive lesion. At times a primary hepatic tumor will cause such obstruction. A diffusely hard and nodular liver suggests a malignant neoplasm, either primary or metastatic, but the same consistency may at times result from cirrhosis. In infancy a diffusely enlarged liver, often with a smooth surface and soft texture, may occur in association with a malignant tumor, as it may with many other causes of hepatomegaly. If a discrete, firm or hard mass is identified, a localized malignant tumor or focal nodular hyperplasia should be considered. If such a mass is soft, a localized infantile hemangioendothelioma or, less probable, a hemangioma or hematoma is suggested. If the lesion is cystic, hamartoma or solitary cyst requires consideration. Calcification in the liver may suggest a metastatic tumor, but calcification may accompany primary lesions as well. Cardiac failure unexplained by cardiac disease may be a sign of infantile hemangioendothelioma.

At operation the lesion must be identified accurately and its potentialities evaluated. A grossly nodular liver is probably the site of a malignant neoplasm, particularly if the nodules are white and fleshy

or variegated and friable. Nevertheless, biopsy should be obtained to rule out other entities. If the gross characteristics suggest solitary cyst, hamartoma or focal nodular hyperplasia, the surgeon should be mindful of their benign nature and avoid heroic attempts to remove them. On the other hand, if a localized lesion is identified as malignant, every effort should be made to resect it, preferably with the entire lobe. A localized, infantile hemangioendothelioma should be excised if feasible, and a somewhat more aggressive attitude is justified than with hamartoma or focal nodular hyperplasia. On the other hand, if the procedure seems formidable enough to jeopardize the patient's life, other means of therapy should be considered.

The clinician should also be aware of the pitfalls which beset the pathologist. The regenerative reactions of hepatic cells and bile ducts may cause confusion in diagnosis, particularly when frozen sections or inadequate material must be interpreted. On the other hand, the benign appearance of certain well differentiated carcinomas may lead to a mistaken diagnosis of adenoma. It is probable that the diagnosis of adenoma should always be suspect until it has withstood the test of time.

The most important factor in the management of liver tumors is close cooperation among all the specialties concerned. A preoperative conference is desirable, attended by pediatrician, surgeon, radiologist and pathologist. At such a meeting the probability of the diagnostic alternatives may be discussed, and the therapeutic implications evaluated for the particular patient. At the time of operation the pathologist and, if possible, the pediatrician and the radiologist should view the lesion in situ. Frozen sections of biopsy material should be examined immediately if indicated, and tissue should always be taken for histologic examination. After the permanent sections have been reviewed a second conference should be held to decide further management. Such a planned approach should minimize the potentially fatal dangers of hasty decisions, assuring in particular that the occasional patient with a benign tumor of the liver will be protected as fully as possible.

SUMMARY

Twenty-nine cases of primary tumor of the liver in infants and children are discussed.

It is emphasized that although the liver is more often involved by malignant tumors, certain rare and benign primary lesions may be self-limited or cured completely.

Helpful features in the differential diagnosis and management of hepatic tumors are presented, and a planned cooperative approach to the management of these lesions is recommended.

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4614 Sunset Boulevard
Los Angeles 27, Calif.

NEUROBLASTOMA

MARTIN BODIAN, M.D.

Although cancer in childhood accounts merely for 0.5 per cent of malignant disease at all ages, it assumes an increasing importance as a cause of mortality. Proportionally, cancer figures have increased as other causes of death have declined, and in recent years malignant neoplastic disease accounted for 15 to 20 per cent of deaths from natural causes of children aged 1 to 14 years in England and Wales.

TABLE 9. *Mortality from Neoplasms in Childhood—England and Wales*

CAUSE OF DEATH	ANNUAL MORTALITY: 1–14 YEARS, INCLUSIVE						
	1949	1952	1953	1954	1955	1956	1957
All natural causes	6412	4687	4002	3814	3897	3606	4020
All forms of neoplasms	853	918	874	734	748	813	618
	12%	19%	20%	19%	19%	23%	17%
Malignant neoplasms	661	748	700	646	661	737	609
	10%	16%	17%	19%	17%	20%	15%

TABLE 10. *Types and Sites of Neoplasms Verified during the Years 1925–58, Inclusive (Excluding Leukaemia and Simple Hamartoma)*

Central nervous system	356
Retinoblastoma	4
Neuroblastoma	129
Ganglioneuroma	15
Nephroblastoma	109
Hepatoblastoma	13
Embryonic sarcoma of urogenital sinus	22
Embryonic sarcoma of other sites	10
Teratoma	81
Malignant tumours of lympho-reticular system	95
Malignant connective tissue tumours	35
Miscellaneous group	38
Total neoplasms	907
Embryonic and teratomatous	518 = 57%
'Adult' type tumours	389 = 43%

From The Hospital for Sick Children, Great Ormond Street, London.

In a review of all verified tumours (excluding leukaemia) occurring at The Hospital for Sick Children in London since 1925, it was found that more than a half (518 of 907) arose in relation to the central or sympathetic nervous system, and neuroblastoma and medulloblastoma proved to be the commonest histological types in this series.

The following survey is derived from a clinico-pathological study of 129 children admitted between 1925 and 1958 with tumours shown by recent histological examination to be neuroblastomata.

AGE AND SEX INCIDENCE

The age at onset was distributed through childhood. The great majority (106) of affected children presented with symptoms during the

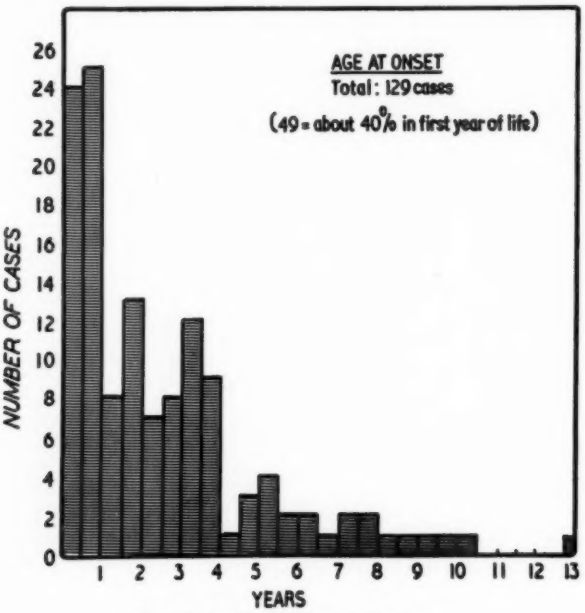

Fig. 48. Incidence of neuroblastoma.

first 4 years of life, and in 49 (40 per cent) of the cases the first manifestations appeared during infancy. The sex distribution was equal (62 males to 67 females).

SITES OF ORIGIN

These tumours may arise anywhere in the sympathetic system or in the adrenal medulla, which has a similar embryological origin. There is,

however, a decided predilection for the adrenal and adjacent portion of the sympathetic chain. In the present series it was established that 48 tumours took origin in the adrenal (with bilateral involvement in 2 cases), and 24 from the adjacent sympathetic chain in the abdomen, whilst in an additional 17 instances the tumours arose from one or other of these 2 sites, though the precise point of origin was uncertain. In all, more than two thirds of all the cases (69 per cent) took origin from an adrenal gland or from the upper abdominal sympathetic chain. Smaller numbers of tumours developed in the cervical (7), thoracic (14) and pelvic regions (10), whilst in one interesting case there were multiple and apparently independent growths arising in the thorax, adrenal, upper abdominal region and pelvis. In the remaining eight instances the site of the primary growth could not be ascertained.

CLINICAL MANIFESTATIONS

Constitutional disturbances such as fever, anaemia, vomiting and general malaise were a frequent presenting feature. The majority of intra-abdominal and pelvic tumours were of considerable size by the time of admission to hospital, being usually readily palpable and often producing considerable abdominal distension. As would be anticipated, cervical neoplasms did not usually reach large dimensions before coming under observation. As a result of their situation, some tumours are likely to produce specific symptoms as a result of pressure; intrapelvic growths, for example, were frequently observed to present with urinary obstruction. Sympathetic paralysis is likely to go unnoted when the tumours are located in the abdomen or pelvis, but in four children in the present series Horner's syndrome was present as a result of involvement of the cervical and upper thoracic portions of the sympathetic chain. Neuroblastoma, like ganglioneuroma, is sometimes of dumb-bell configuration, a portion being situated in the extra-dural space of the spinal canal, and, because of this, symptoms and signs of spinal cord compression may occur or even be the presenting feature, as in 17 of the patients in this survey.

It is a striking feature of neuroblastoma that by the time of presentation the majority of cases show clinical or radiological evidence indicating that the tumour has already invaded adjacent structures, or has metastasised. Such dissemination was detected in 67 per cent of the children of the present series on first admission to hospital. The two primary sites with the smallest evidence of spread were the pelvic and cervical tumours; this may be due to the fact that recognition in these sites is likely to be early in the evolution of the disease. The presence of metastases may be the first indication of the tumour, and since the primary growth may not be obvious, this feature may lead to an initial

TABLE 11. *Clinical Evidence of Tumour Spread at Presentation*

SITE OF PRIMARY TUMOUR	TOTAL NUMBER OF CASES ANALYSED	SPREAD TO LIVER, LYMPH NODES, SKELETON	EPI-DURAL EXTEN-SION	PERCENT-AGE OF TOTAL WITH SPREAD
Adrenals	48	33	1	69%
Abdomen: extra-adrenal	24	14	2	62%
Abdomen ?adrenal; ?extra-adrenal	17	13	3	94%
Thorax	14	5	7	71%
Pelvis	10	2	1	20%
Neck	7	2	2	43%
Uncertain	8	7	1	100%
Multiple	1	0	0	0
Total	129	76	17	67% = ⅔

error of clinical diagnosis, as for example in six children who presented on account of deposits in the limb bones which were thought to be primary growths. Only exceptionally have neuroblastomata been discovered accidentally on routine examination, as in a recent instance of an infant inoculated with B.C.G. vaccine at 10 days of age; a mass in the posterior mediastinum was found on routine X-ray at 6 weeks of age.

PATHOLOGY

Whilst many primary tumours are of considerable size by the time affected children come under observation, this is by no means always the case, and some remain of quite small dimensions despite the presence of extensive metastases. The neoplastic tissue has a tendency to undergo necrobiosis, which on occasion is of such extent that few viable cells remain. This feature may be of significance in relation to the rare but well-authenticated occurrence of spontaneous regression.

In their histological structure, neuroblastomata may show any or all grades of differentiation comparable to that observed in the normal development of the sympathetic nervous system. The most primitive tissue consists of small cells with dark-staining nuclei and only a thin rim of cytoplasm; with greater differentiation the nuclei enlarge and become vesicular, whilst the cytoplasm increases in volume and delicate axonic processes develop, sometimes to such an extent that they form considerable areas of fibrillary structure. Only in the benign counterpart of the neuroblastoma, namely, the ganglioneuroma, are the axons enclosed by sheath cells.

In the present series about a third of the tumours consisted largely or entirely of extremely primitive tissue as described, but in the majority there was an appreciable degree of differentiation rendering identification easy. Not infrequently the extent to which differentiation

occurs varies in different regions of the same tumour, and in a few instances large, well-circumscribed ganglioneuromatous masses were found enveloped by neuroblastic tissue. In addition, differentiation is more commonly greater when the tumour has its origin in the cervical, thoracic and pelvic regions, a feature which may be of some practical importance.

EXTENSION AND METASTASIS

Neuroblastomata are highly invasive and readily infiltrate surrounding tissues. This frequently makes any attempt at adequate surgical removal out of the question, especially in intra-abdominal growths, whose retroperitoneal spread frequently involves adjacent viscera and surrounds major vessels. Metastatic spread occurs readily, by both lym-

TABLE 12. *Autopsy Findings in Neuroblastoma*

PRIMARY SITE OF TUMOUR	TOTAL NUMBER OF CASES ANALYSED	LYMPH NODES		EXTENSION			
		Local	Distant	SKELETON	LIVER	EPIDURAL	OTHER
Adrenals	43	33	33	33	30	4	30
Abdomen: extra-adrenal	16	11	12	10	9	1	5
Thorax	3	2	2	2	0	1	1
Pelvis	1	1	1	1	1	1	1
Neck	4	3	1	2	1	2	1
Multiple	1	1	0	0	0	0	0
Total	68	51	49	48/60	41	9/31	38

phatic and haematogenous dissemination, and surrounding deposits are commonly numerous as well as widespread.

The mode of spread in 68 cases of the present series coming to autopsy is shown in Table 12. Metastases to local and/or distant lymph nodes, to the liver and skeleton, were very common; epidural extension of the tumour was found in more than a quarter of all the cases when searched for. Among miscellaneous organs involved, the lungs were the site of metastases in 14 cases, and the ovaries in 8. Direct or lymphatic invasion of the pancreas occurred in 14 instances, and of the kidneys in 12, whilst in a further 3 cases blood-borne deposits were found in the kidneys. Other rare sites of metastasis were the thymus, choroid plexuses and subcutaneous tissues (2).

PROGNOSIS AND TREATMENT

In the series under survey, 99 out of the total of 129 cases have ended fatally. Death occurred within 6 months from the onset of symptoms

in two thirds (68), and in 90 per cent (90) within 12 months. Nine children survived 14 to 32 months from symptomatic onset. Only 1 untreated child survived 14 months; all others succumbed within 1 year of symptomatic onset of the disease.

Further analysis shows that in 57 instances of these fatal cases no active treatment was undertaken, a fact which is readily understandable in view of the frequency with which extension or metastasis is detected

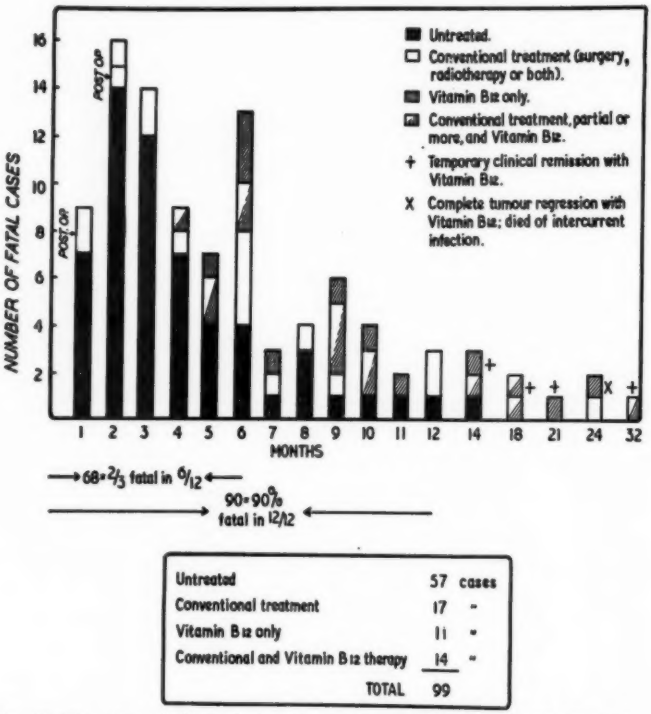
NUMBER OF FATAL CASES
POST OP
POST OP
Untreated.
Conventional treatment (surgery, radiotherapy or both).
Vitamin B12 only.
Conventional treatment, partial or more, and Vitamin B12.
+ Temporary clinical remission with Vitamin B12.
X Complete tumour regression with Vitamin B12; died of intercurrent infection.
MONTHS
68 = 2/3 fatal in 6/12
90 = 90% fatal in 12/12
Untreated 57 cases
Conventional treatment 17 "
Vitamin B12 only 11 "
Conventional and Vitamin B12 therapy 14 "
TOTAL 99

Fig. 49. Duration of illness in fatal cases of neuroblastoma; total, 99 cases.

at the time of presentation (see Table 11). The average survival period in the untreated fatal cases was 4 months from symptomatic onset; the average survival period was 6½ months in those fatal cases submitted to conventional forms of therapy (surgery, radiotherapy or a combination of both), and it was prolonged to 11 months when vitamin B_{12} was either added or given as the sole form of therapy. In a third of the vitamin B_{12}-treated fatal cases (7 of 21), survival extended beyond 1 year, from 14 to 32 months.

In all, 30 patients of the series of 129 are at present surviving.

TABLE 13. *Results of Treatment in Neuroblastoma*

SITE OF PRIMARY TUMOUR	SURGERY		RADIOTHERAPY		SURGERY AND RADIOTHERAPY		VITAMIN B_{12}		SPONTANEOUS REGRESSION
	NUMBER TREATED	SURVIVORS	NUMBER TREATED	SURVIVORS	NUMBER TREATED	SURVIVORS	NUMBER TREATED	SURVIVORS	
Adrenals	4				1	1	12*	1	
Abdomen: extra-adrenal			1		1	1	9†	4	
Abdomen: ?adrenal; ?extra-adrenal			3				5	3	
Thorax			2				9‡	7‡	1
Pelvis	2	2	1	1	1	1	4	3	
Neck	1		1		1	1	2	1	
Uncertain					1	1	5‡	2‡	
Total	7	2	13	1	5	5	46‡	21‡	1

* Temporary regression.
† 1 complete regression—died of poliomyelitis.
‡ Follow-up too short in 4 cases.

TABLE 14. *Neuroblastoma: Survivors after Conventional Therapy*

SITE OF PRIMARY TUMOUR	SECONDARY SPREAD	AGE AT SYMPTOMATIC ONSET (YEARS)	TREATMENT		OBSERVED FOLLOW-UP (YEARS)
			SURGERY	RADIOTHERAPY	
?	Axillary lymph nodes	4 10/12	Removal of axillary deposits	Radium to axilla	21
Pelvis	None	1 5/12	Almost complete excision	+	14½
Pelvis	None	Birth	+	—	3 (lost sight of)
Abdomen: extra-adrenal	None	10/12	+	+	10
Pelvis	None	2/12	+	—	8
Adrenal	None	9/12	+	+	7
Cervical	None	5/12	+	+	7
Pelvis	None	7 3/12	—	+	6½

In one patient cure appears to have been the result of spontaneous regression. The 4-months-old boy presented in 1947 with a mass in the chest, a grossly enlarged liver and a subcutaneous nodule which proved to be a deposit of neuroblastoma. In the absence of any treatment the child is alive and in good health at present (aged 11 years), the only detectable abnormality being residual calcification in the liver and thorax on X-ray, the latter presumably being the primary site of tumour.

A further 8 patients out of a total of 25 so treated are long-term survivors after surgery, radiotherapy or a combination of both.

Reference to Table 14 will show that four of the eight children here included had a pelvic primary tumour (the site with the best prognosis), and that secondary spread was found in one solitary instance only. This child was admitted to hospital in 1933 at the age of 4 years and 10 months with an axillary tumour. The mass was excised and radium applied superficially. Although the growth was originally diagnosed as a lymphosarcoma, recent examination leaves no doubt that it was a lymph-nodal metastasis of neuroblastoma. Radiological examination of the patient at the age of 26 years has failed to show any paravertebral calcification in chest or abdomen, and the site of the primary tumour remains unknown, but whatever its situation, it is unlikely to have been materially affected by the axillary irradiation in the dosage used, and it must be assumed that the primary growth has regressed spontaneously.

The survivors from conventional therapy have been followed up for periods of 6½ to 21 years with the exception of one child with pelvic growth who has been lost sight of. The figures are not very encouraging when it is remembered that patients suitable for radical surgery or radiotherapy form a highly selected group, and that these local forms of treatment are not likely to be used in the majority of cases when there is already evidence of dissemination. In view of the natural history of neuroblastoma, it seems that conventional modes of therapy are unlikely to be curative except in occasional instances when the tumour is detected at an unusually early stage of its evolution. For the majority of cases with widespread dissemination of tumour, the only hope lies in the discovery of an effective chemotherapeutic agent, or alternately of a suitable radio-isotope. At The Hospital for Sick Children, London, 46 unselected cases of verified neuroblastoma have been treated by systemic vitamin B_{12} therapy, with encouraging results.

The Treatment of Neuroblastoma with Vitamin B_{12}

Case I. In November, 1950, a male infant of 7 months was admitted to The Hospital for Sick Children, London, with retention of urine of recent onset. After decompression of the distended bladder by suprapubic cystostomy a large fixed presacral mass was palpable, extending around the rectum, almost filling the pelvis and projecting upwards into the left iliac fossa. Biopsy through the rectal wall yielded neuroblastic tissue showing only minimal differentiation.

The child's general condition was poor, and there was persistent urinary infection. Any attempt at surgical excision of the massive tumour seemed out of the question, and expert opinion considered that radiotherapy was unlikely to be successful. Despite the fact that there was no evidence of metastases, the outlook seemed gloomy.

It so happened that at this time massive concentrates of vitamin B_{12} were made available by the generosity of the Squibb Company, and it was decided by the Tumour Committee (composed of Mr. G. H. Macnab, F.R.C.S., Professor A. A. Moncrieff, C.B.E., M.D., F.R.C.P., and the author) that they should be used on this patient. The reasoning behind this decision was that since vitamin B_{12} was an essential factor for the normal maturation of haemopoietic cells, it might possibly also facilitate the maturation of neuroblastic tissue towards a ganglioneuromatous structure. The reasoning proved wrong and the results unexpected.

After 4 months' treatment the tumour was no longer palpable through the abdominal wall, and the only abnormality was some infiltration in the vicinity of the prostate on rectal examination. Subsequently urine began to be voided per urethram, and the suprapubic tube was removed. After 15 months' treatment, laparotomy was performed. The only remnants of the tumour were 2 minute retroperitoneal nodules on the left of the sacrum, palpable but not visible. Treatment was maintained for a total of 2 years, and the child is in good health and free from recurrence or metastases 8 years from the clinical onset of the disease.

The dramatic tumour regression in this child prompted considerable interest, and the possibility was considered that vitamin B_{12} might have been responsible for it. The only thing to do was to repeat the experiment, and this has been done, with results which tend to show that the response was by no means fortuitous.

A total of 46 cases have so far been included in this therapeutic trial. In all these children the diagnosis has been confirmed histologically. No patient has been denied the possible benefits of surgery and/or radiotherapy. In a considerable number, however, the disease was not considered amenable to orthodox measures, and vitamin B_{12} has been the principal or sole method of treatment. A further 6 cases have been excluded from the survey: 4 of these patients succumbed after only 2 to 12 doses of vitamin B_{12}, and another 2 children were excluded who were long-term survivors after reasonably adequate surgery and/or radiotherapy together with only about a month's treatment with vitamin B_{12}. Of the total of 46 children in the survey, 4 survivors will not be evaluated, for their follow-up period is as yet too short (less than a year).

The dosage of vitamin B_{12} used has in general been 1 mg. on alternate days by intramuscular injection. This dose, which is of course enormously in excess of physiological requirements, was adopted on a purely empirical basis, in the absence of any known rationale.

Since early 1957, the dosage has been further modified: 1 mg. on alternate days was the dose given to infants in the first year of life. In older children the dose was calculated on the basis of 1 mg. per stone (7 kg.) of expected body weight.* The same dosage adopted at the beginning of treatment was maintained throughout the course of at

* Since the English stone is 14 pounds in American weight, the dose would be 0.07 mg. per pound of body weight (0.14 mg. per kilogram).—General Editor's note.

least two years whenever survival permitted. The length of the therapeutic course (about two to three years generally) was determined on the basis of the average survival period of fatal cases of neuroblastoma (see Fig. 49). Whereas conventional anti-metabolites used in tumour therapy are two-edged weapons capable of producing serious or disastrous side-effects, the use of vitamin B_{12}, even in the enormous dosage adopted, has never been attended by any undesirable sequelae.

Of the 46 vitamin B_{12}-treated children in the present series, 20 have succumbed without showing any significant response. It should be observed that frequently these children were already at an advanced stage of the disease when treatment was commenced, and the rapid subsequent course precluded the giving of more than a relatively short course of therapy of 6 weeks' to 7 months' duration, except in one instance when treatment was continued for 15 months. Data referable to these 20 children are given in Table 15. The advanced stage of the disease in this group of cases can be gauged from the fact that all but two had shown clinical evidence of direct, lymphatic or haematogenous spread before inception of vitamin B_{12} therapy.

The age at symptomatic onset varied from 1 year and 3 months to 12 years and 9 months, with an average of 4 years and 8 months. None in this group had a symptomatic onset in infancy. The adrenal was the primary site in 7 cases, the extra-adrenal region in 4, and one or the other in a further 2 instances; altogether an abdominal primary was ascertained in 13 cases. There was one case with a primary cervical tumour, there were two thoracic, one pelvic tumour, and three cases of uncertain primary origin. In nine cases either no treatment was given other than vitamin B_{12}, or else there was merely palliative additional radiotherapy. In all children coming to autopsy there were widespread metastases. Although none of these patients showed any appreciable evidence of clinical response to vitamin B_{12} treatment, evaluation of the survival figures reveals an average of eight months, compared with four months for untreated fatal cases, and with six and a half months for fatal cases treated by conventional methods (surgery, radiotherapy, or both).

Among a further five children who are now dead, four showed definite evidence of temporary tumour regression of six months to two years, and eventually died in relapse. They were all primary adrenal growths with a symptomatic onset in infancy or soon thereafter. All had metastasised prior to inception of vitamin B_{12} therapy. Three had no effective additional therapy, and in one only partial surgery was carried out. Widespread metastases were observed at autopsy. The average survival period in these 4 children was 21 months.

CASE II. The fifth case was a girl who presented at the age of 4 months with weakness of both lower limbs (especially of the left). The child began soiling, and double

TABLE 15. *Neuroblastoma: Vitamin B_{12} Therapy without Obvious Response*

AGE AT ONSET (YEARS)	PRIMARY SITE	SECONDARY SPREAD BEFORE VIT. B_{12}	OTHER THERAPY	SECONDARY SPREAD AT DEATH (P.M.)	DURATION OF ILLNESS (YEARS)
1 3/12	Adrenal	Sk.	S., R.	Ly., Sk., Li., Epi., etc.	10/12
2 10/12	Abdomen: extra-adrenal	Sk.	None	Ly., Sk., Li.	6/12
8 6/12	Cervical	None	S.	No P.M.	5/12
3 4/12	Adrenal	Sk	Palliative R.	Ly., Sk., Epi., etc.	6/12
6 2/12	Adrenal	Sk.	None	Ly., Sk., Li., etc.	11/12
1 9/12	Adrenal	Ly., Sk.	None	Ly., Sk., Li., etc.	7/12
6	Abdomen: ? adrenal; ? extra-adrenal	Epi.	Partial S., R.	No P.M.	5/12
3 9/12	Abdomen: ? adrenal; ? extra-adrenal	Sk.	None	No P.M.	6/12
3 4/12	Abdomen: extra-adrenal	Sk.	R. (to orbit)	Ly., Sk., Li., etc.	9/12
1 6/12	Adrenal	Ly.	R.	Ly., Sk., Li., etc.	4/12
4 2/12	?	Sk.	R. to secondary	No P.M.	10/12
2 9/12	Adrenal	Ly., Li.	S., R.	Sk., Li., Lungs	9/12
2 3/12	Pelvis	Epi.	R. to spine	Ly., Sk., Li., Epi., etc.	14/12
2	Abdomen: extra-adrenal	None	R.	No P.M.	5/12
3 10/12	Abdomen: extra-adrenal	Sk., Ly., etc.	Partial S. to primary. R. to femur (secondary)	No P.M.	5½/12
9 6/12	Thorax	Sk., Ly., Epi.	R. Partial S.	No P.M.	10/12
3 10/12	Thorax	Epi.	R.	No P.M.	8½/12
10	?	Sk.	R. S. to secondary (amputation)	Sk., Epi. No P.M.	18/12
12 9/12	?	Epi.	R.	No P.M.	9/12
3 9/12	Adrenal	Ly., Sk.	None	Ly., Sk., Li., etc.	6/12

Average survival: 8 months (4 in untreated fatal and 6½ in conventionally treated fatal cases).
Average age at symptomatic onset: 4 years and 8 months.
Abbreviations: *Ly.*, lymph nodes; *Sk.*, skeleton; *Li.*, liver; *Epi.*, epidural extension; *etc.*, other metastases; *S.*, surgery; *R.*, radiotherapy.

TABLE 16. *Neuroblastoma: Vitamin B_{12} Treatment—Fatal Cases with Evidence of Tumour Regression*

AGE AT ONSET (YEARS)	PRIMARY SITE	SPREAD BEFORE VIT. B_{12}	OTHER THERAPY	SPREAD AT P.M.	DURATION OF CLINICAL REMISSIONS (YEARS)	DURATION OF ILLNESS (YEARS)
1 4/12	Adrenal	Sk., Ly.	Palliative R. to orbit and later to lymph nodes	Ly., Sk., Li., etc.	2	2 8/12
Birth	Adrenal	Li. (diffuse)	B_{12} for 10/12 only; R. after relapse	Ly., Sk., Li., etc.	7/12	1 2/12
1	Adrenal	Ly., bone marrow	Primary excised; lymph nodes left	Ly., Sk., Li., etc.	6/12	1 6/12
9/12	Adrenal	Li.	None to tumour	Ly., Sk., Li., etc.	1	1 9/12
4/12	Abdomen: extra-adrenal	Ly., Epi.	None	Regression of all tumour	1 11/12	2*

* Died of intercurrent infection (poliomyelitis).

Average survival: 22 months (4 months in untreated fatal, 6½ months in conventionally treated fatal, 8 months in B_{12}-treated fatal cases without obvious response).

Average age at symptomatic onset: 8 months.

Abbreviations: *Ly.*, lymph nodes; *Sk.*, skeleton; *Li.*, liver; *Epi.*, epidural extension; *etc.*, other metastases; *S.*, surgery; *R.*, radiotherapy.

sphincter weakness was suspected. Weakness of the limbs increased in severity. On admission to the Beilinson Hospital, Israel, on May 3, 1954, aged 9 months, the patient was in a good state of nourishment. In the left lumbar region at the level of L 2-3, a hard mass "the size of an orange" was palpable. There seemed to be complete anaesthesia from L 1 downwards, flaccid paralysis of the right leg and almost complete paralysis of the left lower limb. X-rays revealed a round, calcified paravertebral mass to the left of the upper lumbar spine. The body of L 3 was flattened, and there was slight erosion of the left pedicle. Myelography on May 28, 1954, demonstrated a filling defect on the left side of the spinal canal in the upper lumbar region. Laparatomy on June 8, 1954, revealed a left-sided retroperitoneal tumour "the size of an egg," infiltrating muscle and prolonged into the spinal canal through the intervertebral foramina. The tumour was considered inoperable, and only a biopsy specimen was obtained. This was also submitted to the author for examination. It proved to be a neuroblastoma with areas of differentiation towards ganglioneuroblastoma. Adjacent skeletal muscle was infiltrated. There were areas of necrosis and calcification.

The child was admitted on July 7, 1954, to The Hospital for Sick Children, London, under the care of Mr. W. McKissock. There was gross paresis of both lower limbs, especially on the right, with sensory loss over the whole of the right limb. The tumour mass was palpable in the left loin. The anal sphincter was weak. X-ray of the spine showed some collapse of the body of L 3, with considerable enlargement of the intervertebral foramina from L 1 to S 1, and erosion of the pedicles and posterior aspects of the vertebral bodies. The spinal cord and its membranes were displaced to the right from L 1 to L 5. X-ray of the abdomen showed irregular calcification in the region of the tumour. Laminectomy from L 2 to L 5 was carried out on July 15, 1954. The dura was completely covered by purplish grey firm tissue. Owing to the adherence of this tissue to the theca and nerve roots, only a biopsy specimen was removed. Microscopical examination showed neuroblastoma with considerable reactive fibrosis and calcification.

Vitamin B_{12} therapy (1 mg. on alternate days intramuscularly) was initiated on July 16, 1954.

The child was taken back to Israel at the end of September, 1954. By then there was a definite improvement in the power of the lower limbs, and the tone was now the same on both sides. There was still incontinence, with occasional ulceration of the labia. The general health was excellent.

The treatment with vitamin B_{12} was continued and the child brought back to The Hospital for Sick Children in London at the end of June, 1955. Her general condition was excellent. Her weight increase had been constant. The abdomen was not distended, and the bulge noted 10 months previously was no longer present. The tone in the lower extremities was still diminished, particularly on the left side. There was moderate power, better on the left than on the right. Sensation to prick was present over the whole of the left lower limb and on the right side passing up to the mid-thigh. Reflexes were absent, and there was no plantar response. The right ankle was everted and the left ankle inverted. She walked on a wide base, using surgical boots. A skeletal survey revealed no metastases. There appeared to be some consolidation of the body of L 3, but the spinal canal still appeared somewhat widened.

She returned to Israel in September, 1955. She was then alert, active and in good general health. The voluntary movement of both lower limbs had improved, and the tone was now nearly normal.

Her vitamin B_{12} therapy was continued, and she progressed very well until she contracted the bulbar form of poliomyelitis in June, 1957, nearly at the end of the 2 years' course on vitamin B_{12}. She succumbed within 30 hours of admission to hospital. At autopsy only a fibrous scar was found at the site of the former tumour, and complete regression was also established by an exacting histological examination confirmed by the author.

Of the remaining 21 surviving children treated with vitamin B_{12}, 17 show maintained tumour regression for periods of 1 to 8 years, with an

TABLE 17. *Neuroblastoma: Vitamin B_{12} Therapy—Survivors with Maintained Tumour Regression**

AGE AT ONSET (YEARS)	PRIMARY SITE	SECONDARY SPREAD	OBSERVED SURVIVAL (YEARS) FROM COMMENCEMENT OF B_{12}	OTHER THERAPY
7/12	Pelvis	None	8	None
7/12	Thorax	Lymph nodes; epidural	6 3/12	X-ray abandoned (875 r.), resistant; then B_{12} only
Birth	Extra-adrenal	Epidural	2 3/12, then lost sight of	Partial excision
1/12	Neck	None	4 3/12	Recurrence after 400 r., treated with B_{12} only
1	Extra-adrenal	Lymph nodes	3 11/12	Partial excision, radiotherapy
1	? adrenal; ? extra-adrenal	Epidural	4	Viable tumour biopsy after X-ray; then B_{12} only
Birth	? adrenal; ? extra-adrenal	Liver (diffuse)	3 5/12	None
1	Adrenal	Lymph nodes, vulva	3	Partial excision
2 2/12	Thorax	None	2 8/12	Excision; radiotherapy
Birth	? adrenal; ? extra-adrenal	Epidural	2 7/12	None
5 4/12	Thorax	Epidural	2 6/12	Radiotherapy
Birth	Pelvis	None	2 4/12	Partial excision
1 10/12	?	Ribs and ant. chest	2 2/12	Radiotherapy; late partial excision
1 6/12	Thorax	Lymph nodes	2 1/12	Excision
Birth	Pelvis	Lymph nodes	1 10/12	Partial excision
10/12	Extra-adrenal	Lymph nodes; bone marrow	1 8/12	None
6/12	Extra-adrenal	Orbit	1	Excision; radiotherapy to orbit

* Four more surviving cases with follow-up periods of less than 1 year not included. Average age at symptomatic onset: 11½ months. Average survival period so far: 3 2/12 years.

average survival—so far—of 3 years and 2 months. The remaining four cases have been excluded from this survey, for their follow-up period is less than one year.

Thirteen of these children had a symptomatic onset in infancy, and four from 1 6/12 to 5 4/12 years; the average age at onset was just less than 1 year (11½ months). All but four showed direct, lymphatic or haematogenous spread before commencement of vitamin B_{12} therapy. The primary site of growth was an adrenal in one case only, an extra-adrenal site in three, adrenal or extra-adrenal in three children, cervical in one case, thoracic in four, pelvic in three children, and uncertain in one more instance.

In no less than 11 of the 17 cases here discussed either vitamin B_{12} was the sole form of therapy or there was recurrent or residual viable tumour after other forms of treatment.

CASE III. A female infant aged 9 months was admitted on September 5, 1952, under the care of Dr. R. Lightwood. There had been absence of sweating of the left side of the face for 2 months, drooping of the eyelid for 1 month, and the child was not moving her legs much. On examination there was a left Horner's syndrome and spastic paraplegia; hard, discrete, enlarged nodes were present in the left cervical, supraclavicular and axillary regions; the upper left zone of the chest was unduly full, and dull to percussion. X-ray examination revealed a large mass in the upper mediastinum, projecting chiefly to the left and displacing the oesophagus forwards and to the right; there was erosion of the necks of the ribs in the region of the mass, and the intervertebral foramina were possibly enlarged. A supraclavicular lymph node removed for biopsy (September 10, 1952) was found to be replaced by primitive neuroblastic tissue showing only slight differentiation.

Radiotherapy was administered to the thorax for 10 days from September 15, 1952, the total dosage being 875 roentgens, and then abandoned. X-ray of the chest revealed no change in the size of the tumour, which was therefore considered by the radiotherapist not to be radio-sensitive.

Vitamin B_{12} therapy in 1-mg. doses intramuscularly on alternate days was commenced on September 27, 1952, and continued for a total of 2½ years to the end of March, 1955.

By January, 1953, there was considerable diminution in the size of the thoracic tumour on X-ray, and the cervical and axillary lymph nodes had also greatly decreased in size. The general condition remained good, but the paraplegia and Horner's syndrome persisted. Laminectomy was considered, but not undertaken because of a gradual improvement in leg movements. In June, 1953, there were only trivial neurological abnormalities, though some degree of Horner's syndrome still persisted. No evidence of spinal block was obtained on lumbar puncture. She soon began to walk unaided. X-ray of the thorax showed complete disappearance of the chest tumour. The lymph nodes disappeared, and only a few hard calcified tiny nodes were palpable beneath the skin.

The child is now 7 years old and perfectly well 6 years and 3 months after symptomatic onset of the disease. Her left iris is somewhat less pigmented than the right, and there is a slight permanent residue of her Horner's syndrome.

CASE IV. A female infant born on August 1, 1955, was admitted under the care of Mr. G. H. Macnab at The Hospital for Sick Children, London, at 3 hours old with a huge nodular abdominal mass on the right side, extending from the costal margin to the inguinal ligament, and across almost to the left flank, fixed and apparently arising from the loin and indistinguishable from the liver. The swelling was palpable per rectum. The general condition of the baby was good. At laparotomy on August 3, 1955, the mass was identified as liver which showed numerous nodular neoplastic deposits. A biopsy showed massive replacement of liver parenchyma by primitive neuroblastic tissue, as well as infiltration of portal lymphatics with tumour.

There was no evidence of metastasis to skeleton or lungs, and vitamin B_{12} in 1-mg. doses intramuscularly on alternate days was commenced on August 3, 1955, and continued for a total of 2½ years. One month later the abdomen was increasing in size, but by early October, 1955, the mass was definitely decreasing. By February, 1956, the liver edge was barely palpable, and an intravenous pyelogram was normal; there was no calcification in the suprarenal regions.

The child has made uninterrupted progress and is now perfectly well at the age of 3$\frac{5}{12}$ years, without any evidence of recurrence of tumour.

CASE V. A male infant born on May 14, 1956, was noticed to have extreme flaccidity of the lower limbs, and a tumour was felt in the right loin. The child was admitted to The Hospital for Sick Children, London, under the care of Professor

A. A. Moncrieff on June 7, 1956, at the age of 3 weeks. The baby's general condition was satisfactory. He had complete flaccid paralysis of the lower limbs, and there was a large, firm, palpable mass obliterating the right costo-lumbar angle. X-ray examination of abdomen and spine revealed a mass of calcification to the right of the second and third lumbar vertebrae. The spinal canal in this region appeared slightly widened and the pedicles thinned. There was also some suggestion of calcification within the spinal canal. The only other radiological abnormality was the finding of new bone formation along the shaft of the left femur.

Biopsy of the tumour by a posterior retroperitoneal approach confirmed the lesion to be neuroblastoma of primitive appearance with calcification.

Vitamin B_{12} in 1-mg. doses intramuscularly every second day was started on June 16, 1956, and is still being maintained after 2½ years.

By March, 1957, the abdominal mass had become impalpable. There was still complete flaccid paraplegia of both legs without sensation. There was then no erosion of pedicles of vertebrae, and X-rays of long bones and skull were normal

In October, 1957, there was no movement in the legs, and no clinical evidence of recurrence of tumour.

At the end of 1958 there was still no evidence of return of motor power in the lower limbs, nor was there any recurrence of his abdominal tumour. His general condition was excellent.

Discussion

The observation of regressive phenomena in over 50 per cent of the cases treated with vitamin B_{12} is greatly in excess of that occurring spontaneously (probably of the order of 1 to 2 per cent). Even when not sustained, the regression observed has been noteworthy and sometimes dramatic. The long-term results of vitamin B_{12} therapy are encouraging when it is realised that many of the cases treated were beyond the scope of other modes of therapy.

On analysis of this series a striking fact emerges: namely, that regression was observed without exception in cases with the clinical onset in the first year of life.

There were only 5 instances of remission in the older age group, despite the fact that the latter represented 25 out of the total evaluated series of 42 children. It is possible that this represents a reflection of some biological difference of the neoplastic process in relation to age. An alternative explanation may be that, since a standard dosage of vitamin B_{12} had been generally adopted, the concentration achieved in the tissues of older children is inadequate. To elucidate this hypothesis, the dosage is now adjusted in terms of body weight (1 mg. per 7 kg.*), but as this experiment has been in progress only since 1957, a final clarification of this point is not yet possible.

In order to evaluate the possibility of a biological difference between the tumours in children with a symptomatic onset in the first year of life and later, the 58 untreated cases in this series were analysed, and 20 of these were found to have commenced symptoms in infancy. Of these 20, there was only one spontaneous regression. (Spontaneous re-

* 0.14 mg. per kilogram.

TABLE 18. *Fate of 125 Cases of Neuroblastoma in Relation to Metastases, Site of Primary Tumour and Age at Symptomatic Onset*

	UNTREATED		SURGERY AND/OR RADIOTHERAPY		VITAMIN B_{12}	
	FATAL	SURVIVORS	FATAL	SURVIVORS	NO RESPONSE	RESPONSE
Clinical Evidence of Metastases on Presentation						
All metastases	37	1	12	1	18	18
Metastases to skeleton	23	0	6	0	12	1
Total	57	1	17	8	20	22
Site of Primary Tumour						
Abdominal	48		13	2	13	13
Extra-abdominal	6	1	4	5	4	8
Uncertain or multiple	3			1	3	1
Age at Symptomatic Onset						
Birth to 12 months	19	1	4	5		17
Over 12 months	38		13	3	20	5

gression is defined as complete regression of tumour in the absence of any therapeutic procedure; biopsy is of course essential for the establishment of the diagnosis in all such cases.) The average duration of illness in the 57 untreated fatal cases was 4 months; only 9 of these patients survived beyond 6 months, and none beyond 14 months from symptomatic onset. It is perhaps pertinent to mention that of the 19 fatal untreated cases with a symptomatic onset in the first year of life, 11 showed clinical evidence of metastases when first seen, and 5 of the 11 showed skeletal metastases. In 4 of the 19 cases biopsies were performed, and in a further 5, laparotomies.

It is therefore reasonable to conclude that in the untreated series, a third of which presented with symptoms in the first year of life, no biological difference in favour of this group was obvious. Diagnostic surgical procedures did not affect the issue.

Of the 17 fatal cases treated by surgery and/or radiotherapy, 4 were instances of onset in infancy. Three of those showed clinical evidence of metastases, none to the skeleton, when first seen. They survived respectively six weeks, three months, six months and two years from symptomatic onset; in this and other respects they did not vary from the remainder of the group. The over-all survival period in the conventionally treated fatal cases was six and a half months (against four months in the untreated group).

Of the eight survivors after surgery and/or radiotherapy, however, no less than five fell into the group of clinical onset in infancy. But there

were other factors which may have influenced the favourable issue in this group of cases, as well as the age distribution. Seven of the eight cases showed no evidence of metastatic spread, and none spread to the skeleton. This should be compared with the clinical evidence of metastatic spread at first presentation in 37 of the 57 fatal untreated cases (23 of these to the skeleton), and in 12 of the 17 fatal cases treated by surgery and/or radiotherapy (6 of these to the skeleton). Another factor at variance from the fatal cases was the site distribution of the primary tumours: this was two abdominal, five extra-abdominal and one of uncertain origin among the eight survivors in the conventional therapy group. The comparable distribution in the untreated fatal group was 48 abdominal, 6 extra-abdominal, 1 of multiple and 2 of uncertain origin; in the fatal group treated by conventional means there were 13 abdominal and 4 extra-abdominal primary tumours.

Of the 46 children treated with massive doses of vitamin B_{12} solely or in conjunction with surgery and/or radiotherapy, only 42 are analysed, since the follow-up period in the remaining 4 survivors is less than 1 year at present. Among the 22 children who have shown regression of tumour (maintained in 17, transient in 4, and complete but fatal owing to an intercurrent infection in 1), 17 had a symptomatic onset in the first year of life and only 5 thereafter. Eighteen of the children had clinical evidence of metastases on presentation (only one to the skeleton, and this was an example of temporary regression). The distribution pattern of the primary tumour was 13 abdominal, 8 extra-abdominal and 1 of uncertain origin.

Of the 20 children who showed no obvious clinical response to massive vitamin B_{12} therapy, none was of infantile symptomatic onset. Eighteen showed clinical evidence at presentation of metastases (12 of these to the skeleton), and the primary site distribution was 13 abdominal, 4 extra-abdominal and 3 of uncertain origin. Although this group of 20 fatal cases showed no obvious signs of clinical remission, the average period of survival was prolonged to 8 months (4 months in the untreated fatal group and 6½ months in the conventionally treated fatal group).

No child with a clinical onset of disease in the first year of life has failed to respond favourably to massive vitamin B_{12} therapy, and the age at which symptoms appear is the most important individual prognostic factor in this series. This biological age factor did not become overt in the untreated fatal group, but seemed to be contributary (amongst other factors) in the group treated by surgery and/or radiotherapy, although four of the nine infants in this group failed to respond. This gradient in biological behaviour in the age group under 1 year becomes obvious when one compares the average survival period of the fatal cases with onset in infancy: it was 3 months in the un-

treated group (19 cases), 8½ months in the group treated by surgery and/or radiotherapy (4 cases), and 19 months in the vitamin B_{12} group (4 cases, all with clinical remission).

The finding of clinical evidence of metastases at first presentation was not of prognostic significance in the vitamin B_{12} group, except that maintained tumour regression was not observed in the presence of clinically obvious skeletal metastases (temporary regression for two years was seen in one instance). No statement can yet be made about the significance or otherwise of the observation of tumour cells in bone marrow in the absence of clinically overt bone metastases. Undoubtedly the almost total absence of metastases in the small group of survivors with conventional therapy was an important contributary factor in addition to the age incidence.

The evaluation of abdominal and extra-abdominal sites of the primary tumour as a prognostic factor is not quite clear, although there was a much higher incidence of the extra-abdominal tumours in the small group of conventionally treated cases, but this was also associated with a favourable set-up regarding age incidence and metastases.

The proportion of extra-abdominal to abdominal tumours in the vitamin B_{12} group with remission was somewhat higher than in the untreated, vitamin B_{12}-treated and conventionally treated fatal groups, but the significance of this finding is not convincing. Another point of prognostic importance arises from Table 19. By far the smallest proportion of survivors was found among the children with primary adrenal tumours (2 out of 49, or 4 per cent).

Finally, it should be mentioned that an attempt was made to relate the degree of differentiation of tumours to prognosis. Such an attempt is bound to be fraught with difficulties, since many of the tumours show considerable variation in differentiation from area to area, and unless adequate representative portions are examined, no statement of value can be made. Hence small biopsy specimens are useless from this point of view. Even when the entire tumour is available for examination, it is difficult to apportion prognostic significance in quantitative terms of relatively primitive and mature tissues. Notwithstanding all these objections, there was some tendency to a higher degree of differentiation in the tumours arising in the chest and pelvis when compared with tumours of other sites.

Reference was made by the author to published data on neuroblastoma, notably to the recent review article by Sutow,[6] and to the series recorded by Farber,[2] Phillips,[5] Gross,[3] Wittenborg,[7] and Koop and his colleagues.[4] Moreover, the author has had the advantage of personal communications from many paediatric centres in the United States, in particular from Cincinnati (personal communication from Dr. A. J.

TABLE 19. *Fate of 129 Cases of Neuroblastoma Related to Site and Therapy**

SITE OF PRIMARY TUMOUR	UNTREATED		CONVENTIONAL THERAPY		VITAMIN B_{12}		OVER-ALL TOTAL	
	NUMBER	SURVIVORS	NUMBER	SURVIVORS	NUMBER	SURVIVORS	NUMBER	SURVIVORS
Adrenals	27	0	10	1	12	1	49	2
Abdomen: extra-adrenal	12	0	2	1	9	4	23	5
Abdomen: ?adrenal; ?extra-adrenal	9	0	3	0	5	3	17	3
Cervical	2	0	3	1	2	1	7	2
Thorax	3	1	2	0	9	7	14	8 (3*)
Pelvis	2	0	4	4	4	3	10	7
Uncertain	2	0	1	1	5	2	8	3 (1*)
Multiple	1	0	0	0	0	0	1	0
Over-all total							129	30

* 4 cases with follow-up of less than 1 year.

McAdams), from New Orleans and from San Francisco, as well as from various paediatric units in Great Britain.

On the whole, there is a good measure of agreement about a more favourable course of the disease in the younger age groups irrespective of the form of treatment applied. No homogeneous series of cases has yet been produced, nor is it claimed that the present investigation is ideal in that respect. Nevertheless, the evidence here given of unexceptional remission of tumours in infancy in the vitamin B_{12} group is highly significant in relation to the background information from untreated cases in this hospital, and in relation to data obtained from the literature and from personal communications.

We are at present ignorant of the mode of action of vitamin B_{12} on neuroblastoma. The hypothesis on which vitamin B_{12} was originally used, that it might induce maturation from neuroblastoma to ganglioneuroma, suggests that the tumour would persist, though in a changed histological form. In fact, this is not what is observed. When remission occurs, it is associated with progressive shrinkage of tumour, which, so far as can be observed, is appreciable within two or three months, and proceeds in favourable cases to complete disappearance. The process is a frank regression.

Such regression occurs on occasion spontaneously, and its exact mode remains conjectural. Neuroblastoma, when of any size, shows considerable haemorrhagic necrosis indicative of a precarious balance between nutritional requirements and supply. Interference by a variety of means may serve to tip the scales in the direction of tumour destruction, such as surgery, even short of complete removal, irradiation and chemotherapy. It is possible that vitamin B_{12} represents yet another way of stimulating the tendency of self-destruction of neuroblastoma, possibly by direct interference with growth, or even by stimulating growth in excess of available nutrition.

A study of the problems concerning the mode of action of vitamin B_{12} on neuroblastoma is at present in progress, and it is hoped that a better understanding of the fundamental biological processes will be possible in the not-too-distant future.

SUMMARY

A study of the natural history of neuroblastoma was based on an analysis of 58 untreated cases, and this information was used as a background to the evaluation of (1) local forms of treatment, i.e., surgery and/or radiotherapy, and (2) a systematised form of treatment, namely, massive doses of vitamin B_{12} with or without surgery and/or radiotherapy. The single most important prognostic factor was found to be the age

at symptomatic onset of the disease, the critical division being less than or over the age of one year.

This biological difference was not overt in the untreated group, which included 20 infants under 1 year. Only 1 of these survived, the sole instance of complete spontaneous regression among the 129 children in the whole series. The average period of survival among the 19 fatal cases in infancy was merely 3 months.

The conventionally treated group of 25 children included 9 infants, 5 of whom—all without any evidence of metastases—survived. Of the four fatal cases, three showed evidence of secondary spread, and the average survival period among the fatal cases in this group was eight and one half months. Survival seemed to be of a high order when onset in infancy was coupled with absence of metastases.

Of the vitamin B_{12}-treated group of 46 children, 4 were not evaluated, owing to their follow-up period being less than 1 year. Of the 42 remaining children, 17 manifested the disease in infancy, and all of these showed clinical remission, in spite of secondary spread, except to the skeleton, in all but 4 instances. Maintained remission for periods of 1 to 8 years in 13, complete regression of tumour in a child succumbing to poliomyelitis, and temporary remission with ultimate recurrence of disease and fatal issue in 3 further cases is the score at present. The average period of survival among the 4 fatal cases with onset in infancy in this group was 19 months. Remission of tumour in the age group over 1 year was much less common; it was observed in 5 of the 25 cases so defined.

The mechanism of the action of vitamin B_{12} on neuroblastoma is not known, but it is felt that it is a useful therapeutic agent of systemic action in this systematised disease, whether applied solely or in conjunction with surgery and/or radiotherapy. It would appear that it greatly enhances a biological tendency of the tumour to regress, particularly in the group of children with a symptomatic onset in the first year of life. This regression is certainly therapeutically induced and not a spontaneous phenomenon. The latter is, however, well authenticated, but of very rare occurrence, and almost always restricted to infants in the first year of life.

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It is with gratitude that the author acknowledges a grant from the British Empire Cancer Campaign in support of the work of the Tumour Research Fellowship previously held by Dr. L. L. R. White, who was closely associated with the work here reported. To my fellow members of the Tumour Committee, Mr. G. H. Macnab and Professor A. A. Moncrieff, I wish to express my gratitude for their support of the study of neoplastic diseases in childhood ever since its inception. Thanks are also due to all the members of the Medical and Surgical Staff of The Hospital for Sick Children for permission to include records of the children in this series who had been under

their care. Finally, I am greatly indebted to Mr. Derek Martin and the staff of the Department of Medical Illustration for the preparation of the illustrations and tables.

EDITOR'S NOTE. The present clinic on Neuroblastoma by Dr. Martin Bodian is an extremely interesting and provocative one and deserves careful consideration. It should be recognized, however, that treatment of neuroblastoma by vitamin B_{12} is not the usual method used in most centers at present. As noted by Dr. Bodian, the better survival rates of infants as compared with older children with neuroblastoma has been observed by others. Horn, Koop and Kiesewetter[4] reported 12 of 17 patients under 12 months of age to be living without clinical evidence of disease 14 months or longer after the diagnosis was established. Although they advocated removal of as much of the neoplasm as possible, in a number of these infants the removal was incomplete. Experiences such as this must be considered in evaluating the role of vitamin B_{12} in patients (and especially in infants) with this rather unpredictable neoplasm. Until further data are available it might be well to note Dr. Bodian's conservative approach as indicated by his statement: "No patient has been denied the possible benefits of surgery and/or radiotherapy." J. B. A.

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Great Ormond St.
London, W.C. 1
England

RENAL TUMORS

SAMUEL L. CRESSON, M.D.

GEORGE P. PILLING, IV, M.D.

Renal tumors comprise approximately 20 per cent of all neoplasms in children.[12] As a cause of death, renal tumors outrank poliomyelitis, whooping cough, syphilis, scarlet fever and measles together in children from one to four years of age.[13] These tumors are not rare, nor is their prognosis as hopeless as it was thought to be two decades ago.

Renal tumors are being found earlier, and more immediate therapy is being carried out, because physicians are more aware of the frequency of malignant tumors in infants and children. Tumors confined to the kidney usually present at asymptomatic abdominal masses that grow rapidly and metastasize early. There is usually no previous warning of their presence. All physicians examining infants and children should, therefore, routinely examine the abdomen for tumors as one examines an adult woman's breast for carcinoma.

All infants and children who present with abdominal masses must be studied to rule out retroperitoneal neoplasms, although hydronephrosis is the most common abdominal mass found in infancy and childhood.

The purpose of this paper is to present a practical evaluation of the diagnostic and therapeutic approaches to renal tumors in infancy and childhood. Since the majority of renal neoplasms in children are embryomas (nephroblastoma), we shall emphasize these tumors in our discussion and consider the rarer kidney tumors only briefly.

From the Surgical Service, St. Christopher's Hospital for Children, and the Departments of Pediatrics and Surgery, Temple University School of Medicine, Philadelphia.

NEPHROBLASTOMA

Historical

A review of the English literature reveals that the first case of nephroblastoma was described by Thomas F. Rance[54] in 1814. The second recorded case was described by Ebenezer Gairdner[25] in 1828. Both tumors were examined at autopsy and diagnosed as "fungus haematodes."

In 1872 Eberth[20] first described the mixed histologic structure of nephroblastoma, and in 1876 Kocher[20] performed the first transperitoneal nephrectomy for this lesion. One year later, in 1877, Jessop[20] performed the first successful nephrectomy for nephroblastoma. Although there are several earlier reports in the European literature, it was not until 1899 that Wilms[76] in his classic paper described this type of tumor in detail.

Nephrectomy was the only treatment until Herman[20] in 1915 started using radiation therapy in the postoperative period and Geraghty[20] in 1923 used preoperative radiation. Gross and Neuhauser[31] showed that with the advent of postoperative radiation they were able to increase the 2-year survival rate of their patients from 32.2 to 47.3 per cent. At present nephrectomy and various combinations of roentgen therapy and nephrectomy are the most commonly used methods of therapy for nephroblastomas. Chemotherapy is being evaluated in conjunction with roentgen therapy and nephrectomy in some institutions.[9, 38, 70]

Histogenesis

In reviewing the many theories[6, 58] of the histogenesis of nephroblastoma, we believe with other authors[28, 53, 74, 76] that these tumors are formed from mesodermal cell rests.

The cell rest theory was first suggested by Cohnheim[8] and later by Wilms[76] in 1899. Wilms reasoned that, since varied tissues enter into the formation of the tumor, these neoplasms must arise from a very embryonic type of cell that has multipotentialities for forming numerous tissues and structures. Geschickter and Widenhorn[28] state:

> Approximately two thirds of all Wilms' tumors contain only those microscopic elements of spindle cells and early tubule formation which can be found in the normal kidney or in the zone of development just beneath the capsule of the kidney in normal infants a few months after birth. The majority of these tumors, therefore, are neither teratomatous nor mixed, but represent a neoplastic exaggeration of the normal developmental processes occurring in the growth zones of the renal cortex in later fetal life or in the first few months after birth. For this reason the term embryomal nephroma (introduced by Feldman) is a particularly apt one for these neoplasms.

Such cell rests have been encountered by Wells,[74] Potter[53] and Macgregor.[47]

Clinical Manifestations

Age Incidence. The diagnosis of nephroblastoma is usually made under five years of age, the average age being three years.[1, 35, 62, 76] Hartenstein[33] collected 13 cases of patients with embryoma which were apparent in the newborn period and added 1 of his own. There have been 97 nephroblastomas reported in adults,[64] the oldest of whom was 80 years of age.

SEX INCIDENCE. In his monograph Wilms[76] records an equal sex incidence, an equality supported in all subsequent series of case reports of patients with embryoma.

LOCATION. Each kidney is equally affected. There are 44 cases of bilateral involvement reported which are probably authentic.[1] The incidence of bilateral involvement is significant, but difficult to evaluate because histologic proof of the diagnosis is often lacking, and some cases may represent metastatic spread. The incidence of bilateral involvement is stated as ranging from 7.2 per cent[76] to 2 per cent.[20]

HEREDITARY FACTORS. The occurrence of nephroblastoma in more than one member of a family is rare. Maslow[43] reports three proved cases and a probable fourth in one family. Chapian[15] and Collins[17] have each reported two proved cases in siblings. Gaulin[27] found unilateral tumors in the contralateral kidneys of identical twins. Scott[64] states that there have been five authentic reports in which more than one member of a family has been affected with nephroblastoma.

Signs and Symptoms

The maxim that "*every solid mass in an infant or child should be considered as a malignant tumor until histologically proved otherwise*"[13] has been stressed since Walker's[71] description in 1897. The majority of patients with Wilms' tumor are first seen because of abdominal enlargement which may be noticed because the infant's clothes suddenly become too tight. It is probable that a congenital rest of cells suddenly begins to grow and invades beyond its capsule. In a vast majority of instances the presenting mass is of huge proportions and has already metastasized in 20 to 30 per cent of the patients.[22]

Other signs and symptoms probably are late manifestations of tumor growth. Certainly weight loss, pallor, lethargy and anorexia, which are commonly seen, are associated with large growths. Fever has been noted in association with embryomas in 20 per cent of collected series.[20] The incidence of hypertension is difficult to evaluate because the blood pressure is not recorded in many reported cases. Synder[68] reports its presence in 72 per cent of his 47 patients, and Silver[67] in 87.5 per cent. It probably is due to ischemia of the kidney, since no pressor substance has been found in resected specimens. The hypertension is usually relieved by nephrectomy.[10, 19]

Urinary symptoms and signs are usually minimal or absent. Flank pain is rare, occuring in only 10 per cent of patients. Hematuria is noted in approximately 10 per cent of patients with Wilms' tumor.[1, 20] It is caused by invasion of the tumor into the renal calices or pelvis and is a poor prognostic sign. Nesbit[50] and Scott[63] reported 100 per

cent mortality in their patients who manifested hematuria, and others report a high mortality rate.[29, 38]

The significance of trauma in initiating growth changes in renal tumors is debated. It seems probable that trauma initiates hemorrhage into an already diseased kidney, causing its rapid enlargement and drawing attention to the area by pain, tenderness and the palpation of the previously unrecognized tumor.

Diagnosis

Since the appearance of an abdominal mass is the most common presenting sign of renal neoplasm in children, early diagnosis depends

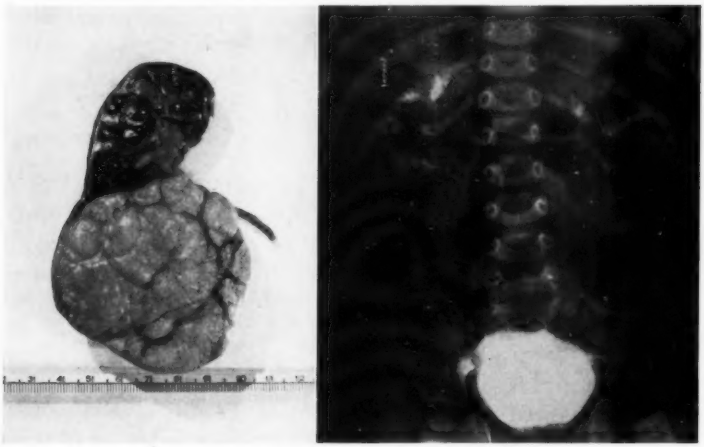

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Fig. 50. A, Right kidney and nephroblastoma removed surgically from a 13-month-old boy. An asymptomatic abdominal mass had been discovered by his pediatrician during a routine physical examination. (From W. E. Nelson: *Textbook of Pediatrics.*) *B*, Intravenous urogram on same patient illustrating distortion of the lower calices of the right kidney. Patient is living and well without evidence of metastases 5 years after therapy.

on frequent and thorough abdominal examinations of all infants and children. To facilitate an adequate appraisal of the abdomen of an infant, the parents should be urged to bring a bottle of formula to the physician's office, and every office and clinic should keep sterile nursing bottles filled with sugar and water on hand. If the abdominal examination is performed first, using a dry warm hand while the infant is contentedly sucking, early recognition of an abdominal mass is facilitated. One most frequently palpates a large, globular, firm, nontender mass in either hypochondrium which usually does not cross

the midline (Fig. 50). Its mobility may vary with respiration, and it is frequently impossible to differentiate it from an enlarged liver, spleen or other organs. Tumor nodules in the liver are rarely palpable in a patient with Wilms' tumor. They are more frequently present in patients who have neuroblastoma. Osseous, superficial lymph node and skin metastases are so rare in Wilms' tumor that their presence should lead one to suspect neuroblastoma or lymphoma. The chest is usually clear to physical examination, even in the presence of multiple metastatic nodules in the lungs.

The discovery of an abdominal mass necessitates an immediate investigation of its nature. Roentgen examination should be performed immediately. We routinely request immediate abdominal films, an intravenous urogram, a chest x-ray and skeletal survey. The plain film of the abdomen will be helpful in outlining the mass, especially if a lateral projection is included. Usually the colon is displaced downward by an enlarged liver, whereas in renal tumors it extends anteriorly, the flexure is opened widely, and the colon is wrapped around the mass.[52] Calcification is present in only 10 to 15 per cent of embryomas[8, 69] and may be dense and occur in concentric rings. A large percentage of neuroblastomas, up to 57 per cent in some series, will contain calcium in a stippled or flaky configuration.[69] Other renal lesions such as hypernephroma and hematoma may also calcify.

Excretory urography is essential for the evaluation of most abdominal and all renal masses in children. Although the contrast medium can be injected by the subcutaneous or intramuscular route, intravenous administration is preferred. It is recommended that 0.7 cc. of 50 per cent Hypaque per kilogram of body weight be injected after testing for sensitivity by giving a small dose intravenously. After the injection of a contrast medium the patient is urged to drink a carbonated beverage or formula from a nursing bottle. This distends the stomach with gas so that the kidneys, if they are in normal or near normal position, are clearly outlined through the clear gas bubble. The purpose of performing an intravenous pyelogram is threefold: first, to determine whether and how the mass involves the kidney; second, to demonstrate the presence of a kidney on the opposite side; and, third, to evaluate its function and to determine whether bilateral tumors are present. Although a nephroblastoma causes no pathognomonic roentgen changes, one characteristically sees evidence of the presence of an intrarenal mass which distorts and occasionally invades the pelvis and calices (Fig. 51). The presence of such a lesion usually represents an embryoma, but the exact nature of the mass cannot be verified by roentgen examination (Fig. 52). Excretory function is usually well preserved in embryoma, but will usually be absent or delayed in the hydronephrotic kidney. Hydronephrosis is usually caused by a con-

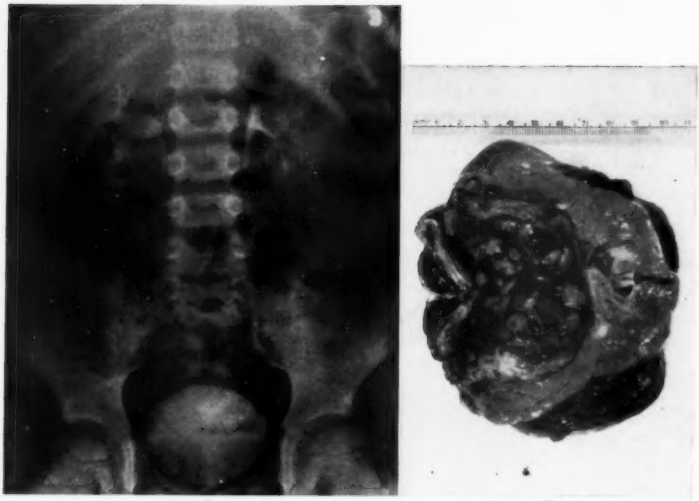

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Fig. 51. A, Intravenous urogram illustrating distortion of the left renal calices with invasion of the pelvis of the kidney in a five-year-old boy. B, Operative specimen of the left kidney and nephroblastoma from the same patient, showing invasion of the renal pelvis and ureter by the tumor. Patient is living and well without evidence of metastases 6½ years after therapy.

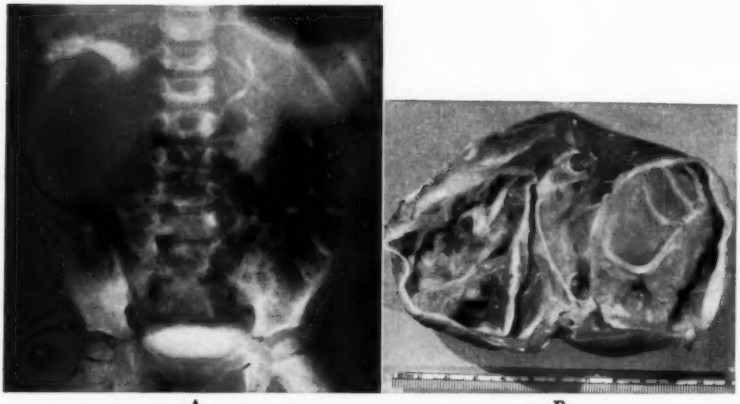

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Fig. 52. A, Intravenous urogram which illustrates distortion and displacement of the calices of the right kidney by an intrarenal mass. The abdominal mass was asymptomatic in this 3-year-old girl. B, Surgically removed right kidney from same patient. The tumor proved to be a benign multiloculated cyst. (From J. B. Arey: Cystic Lesions of the Kidney in Infants and Children. *J. Pediat.*, 54:432, 1959.)

genital lesion blocking the excretory system or may be caused by renal invasion of a neuroblastoma (Fig. 53).

If adequate visualization of both kidneys is not obtained by intravenous urograph, retrograde investigation must be performed so that clear visualization of both kidneys and ureters is available for accurate evaluation.

Since 20 per cent or more of patients with Wilms' tumor have pulmonary metastases at the time the diagnosis is made, a pretreatment chest x-ray is also mandatory.[13] Metastatic lesions characteristically

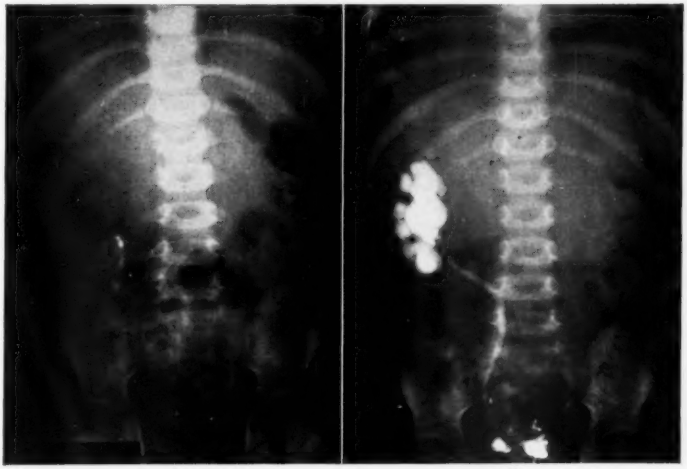

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Fig. 53. A, Intravenous urogram which demonstrates hydronephrosis, displacement and delayed drainage of the right kidney. The left kidney was normal. This 2½-year-old girl had a large intra-abdominal tumor mass. B, Retrograde pyelogram on the same patient which clearly defines the hydronephrosis due to invasion of the right kidney by an extrarenal mass which proved to be a neuroblastoma.

occur in the lung fields. They are round and discrete with somewhat indistinct borders, moderately dense to x-ray penetration, and may be single or multiple. They are usually unilateral when first visualized (Fig. 54). Hypernephromas also metastasize to the lung, but are rare in children.

The skeletal survey is performed primarily to differentiate the embryoma from a neuroblastoma which metastasizes to bone. We have not encountered any osseous metastases from embryomas, but Willis[75] states that they may occur, and we have found nine reports in the literature,[18, 39, 48, 66, 68] although histologic proof is not mentioned.

The use of needle biopsy to obtain the histologic diagnosis of nephroblastoma is unwise. The negative biopsy may mean only that a

Fig. 54. Multiple metastatic lesions in the right lung from a nephroblastoma of the left kidney. The primary lesion had been excised from a 7½-year-old boy 7 months previously, and he died 22 months after nephrectomy.

normal portion of the kidney was tested and does not exclude the presence of a tumor. Needle biopsy is always a risky procedure in an active and uncooperative child. These tumors are highly vascularized, and this procedure may be followed by severe hemorrhage. In Dean's[2] experience local recurrences of the tumor followed needle biopsy in all his cases, and Nesbit[50] joins him in condemning this procedure.

Treatment

There are five methods of therapy commonly used for the treatment of patients with Wilms' tumor. They are (1) nephrectomy alone, (2) roentgen therapy alone, (3) preoperative roentgen therapy plus nephrectomy, (4) nephrectomy followed by postoperative roentgen therapy, and (5) preoperative roentgen therapy followed by nephrectomy and subsequent postoperative roentgen therapy. Each of these five methods may be combined with tumor chemotherapy. There are no recorded cases in the literature of spontaneous cure of patients with histologically proved embryomas.

As Abeshouse[1] states: "The necessity for standardizing the treatment of Wilms' tumor should be apparent to all in view of the wide diversions of opinion arising from the results reported in the past twenty years." To this we would add a plea for the accurate and detailed recording

of the therapeutic regimens used so that results can be properly evaluated. We shall summarize these five basic methods of therapy and then discuss their advantages and disadvantages.

Nephrectomy Alone. The importance of radical nephrectomy in the treatment of patients with nephroblastoma is unquestioned. We agree with Walker[71] and Ladd,[44] who stress the importance of using a transabdominal approach, and this is the method of choice of the majority of surgeons responding to Abeshouse's[1] questionnaire. This approach permits early ligation of the renal artery and vein and therefore diminishes the possibility of dislodging tumor emboli into the circulation. It also allows one to examine the opposite kidney manually and, if advisable, to identify the opposite adrenal. Hepatic, lymphatic, peritoneal and other possible local sites of extension can be determined, and other intra-abdominal abnormalities may be sought for. If the tumor involves the vena cava or aorta or other essential structures, a better evaluation of the necessary steps to remove it is possible. All the perirenal fat and lymph nodes should be removed. Unless it is grossly involved, the adrenal is usually not removed, but Ackerman and Regatta[2] advise that ipsilateral adrenalectomy be performed if the tumor arises in the upper pole of the kidney. Kruse,[41] also, advises removing the adjacent adrenal and spermatic vessels because of the common venous drainage as shown by Hollingshead[37] in animal experiments. The limit of the extension of the tumor is marked by Cushing silver clips so that the area to receive postoperative roentgen therapy can be accurately outlined.

From 1930 to 1939 Ladd[21] treated 31 patients by nephrectomy alone and obtained a 2-year survival rate of 32.2 per cent.

Other surgeons, notably Nesbit,[50] prefer the classic retroperitoneal lumbar nephrectomy incision. Recently a thoracoabdominal approach has gained popularity, particularly for tumors arising in the upper pole of the kidney.

Radiation Alone. Radiation therapy to patients with Wilms' tumor is commonly administered as conventional deep roentgen therapy. This may be administered in the range of 200 to 250 kilovolts, 15 to 20 milliamperes current, with a target skin distance of 50 cm., filtered through 0.5 mm. of copper alone or combined with 1 mm. of aluminum to produce a half-value layer of 1.62 mm. of copper. Postoperatively we administer a tumor dose calculated at the midplane of the abdomen to 2500 roentgens over a 3-week period, alternately using anterior and posterior ports over the tumor bed. The amount of radiation recommended by various authors varies from 1500 to 3000 roentgen-tumor dose. Because the factors used are often not stated clearly, an accurate evaluation of the efficacy of different treatment schedules is impossible.

PREOPERATIVE ROENTGEN THERAPY FOLLOWED BY NEPHRECTOMY. Fewer patients have been treated by preoperative conventional deep roentgen therapy followed by nephrectomy than by the other four methods. It has been used to decrease the size of large lesions which were considered inoperable when first seen. In Harvey's[35] series this method of therapy obtained an 18.5 per cent 2-year cure rate, which was an increase of 3 per cent over therapy by surgery or x-ray alone, but the number of patients treated in this manner was probably too small for statistical analysis. In Scott's[63] collected series of 81 patients so treated, 21 were living and well 2 years after therapy, giving a 2-year survival rate of 25.9 per cent. This compared with 23.9 per cent for nephrectomy and postoperative therapy and 18.8 per cent for nephrectomy alone.

NEPHRECTOMY PLUS POSTOPERATIVE RADIATION. This method of therapy has been the most popular one in recent years. In 1950 Gross and Neuhauser[31] reported an over-all 2-year survival rate of 47.3 per cent in 38 patients treated by this method. Credit is given to Ladd, whose intensive effort was successful in reducing postoperative mortality rate at the Boston Children's Hospital from 23 per cent of 27 cases treated from 1914 to 1930 to zero in 31 cases treated from 1931 to 1939 by nephrectomy alone. The only major change in treatment during the period 1940 to 1947 was the addition of postoperative roentgen therapy to the therapeutic regimen.

Nesbit and Adams'[50] cure rate of 50 per cent in 16 patients treated in this manner does not include 11 other patients seen by them during the same period of time who were presumed to have embryoma, but were not treated by nephrectomy. Other authors[32, 41] report 2-year survival rates ranging from 24 to 38.8 per cent. In Harvey's collected series the 18-month survival rate of patients treated by this method was 30 per cent.[32]

PREOPERATIVE RADIATION, NEPHRECTOMY AND POSTOPERATIVE RADIATION. During recent years, and especially since Silver's[67] report in 1947, this method of therapy has gained in popularity. It combines the alleged advantages of preoperative roentgen treatment previously mentioned with those of radical nephrectomy and postoperative radiation. Different treatment schedules are recommended. When using this method of therapy, some authorities[18, 50, 73] recommend a short preoperative course of radiation of 1500 to 2000 roentgens administered over a period of 1 to 2 weeks and followed by immediate nephrectomy. Other authors[6, 11, 51] recommend a longer course of therapy and a still longer delay before nephrectomy is performed. Attempts to evaluate accurately the relative value of this type of therapy are fruitless. Too many authors report on too few cases treated by too many methods.

Ng[51] in his supplemental report to Silver's[67] article shows a 2½-year survival rate of 87.5 per cent in 8 patients so treated, Creevy[20] 47 per cent of 13 patients, and Scott[63] of his collective series a 31.8 per cent 2-year survival rate. Other authors[23, 24, 31, 66] report a 100 per cent mortality in a total of 14 patients treated by this method.

Treatment of Metastases. Metastatic spread of nephroblastoma may be local or distant. Local recurrence is less common and occurs in the regional lymph nodes, peritoneum, liver and adjacent structures. Baker[5] and Sauer[59] have each reported on a newborn infant with skin metastases. Distant metastases usually occur in the lungs, 90 per cent of them appearing during the first year after therapy to the primary lesion.[2]

Until recently roentgen therapy was the most common treatment administered to pulmonary metastases. There are many reports[20, 26, 51] of presumptive cures of metastatic pulmonary disease by roentgen therapy alone, but we have been unable to find a recorded case in which histologic proof of the cell structure of the pulmonary lesion was obtained. However, since there have been at least seven cures of histologically proved primary nephroblastoma by roentgen therapy, it may be presumed that some metastatic lesions can be eradicated by roentgen therapy.

Nesbit[46] reports the successful surgical removal of a metastatic pulmonary lesion 17 years after the primary nephroblastoma had been excised. Recently Richardson[56] presented before the Section on Surgery at the American Academy of Pediatrics the results of a survey he had conducted on the value of pulmonary resection for metastatic lung disease. Thirteen of 17 patients who had undergone pulmonary resection for metastatic nephroblastoma had survived more than 2 years, and 4 had survived more than 5 years.

The role of nitrogen mustard in controlling or preventing metastases is being evaluated.[9, 38, 70] The results are inconclusive at present.

Discussion of Therapy. Early radical nephrectomy is the basic method of therapy for nephroblastoma. This should be performed as described above, and in Ladd's[31] series of 31 cases treated between 1931 and 1939 produced a 2-year survival rate of 32.2 per cent.

There is ample proof that conventional roentgen therapy can usually decrease the size of the tumor mass preoperatively and increase the survival rate significantly when used postoperatively. Roentgen therapy is a dangerous but valuable method of treatment and must be administered with skill and caution. Complications following its use vary from fatal agranulocytosis,[7] radiation nephritis,[35] pneumonitis,[55] and colitis with fatal ulceration to growth changes in the vertebra and ilium which sometimes require corrective orthopedic surgery. Sterilization, especially

in the female, is a possibility, and the potential carcinogenic effect is unknown. Preoperative roentgen therapy is thought by some[44] to increase the possibility of blood-borne metastases by causing necrosis of the tumor and unnecessarily delaying immediate nephrectomy. Others[35, 18, 51, 73] believe that the decrease in the size of the tumor and the fibrosis which results from the preoperative roentgen therapy decrease the likelihood of vascular thrombi and facilitate nephrectomy. The objection to administering preoperative roentgen therapy without obtaining a positive tissue diagnosis must be weighed against the statistics that 80 to 90 per cent of collected series of retroperitoneal tumors are malignant growths, the majority of which are radiosensitive.[68] The best method of administering preoperative roentgen therapy is unknown.

The value of the routine administration of roentgen therapy during the postoperative period would seem to be unquestionable since the increase in the 2-year survival rate from 32.2 to 47.3 per cent, which increase Gross and Neuhauser[31] attribute solely to its use. Yet we and others[1, 38] have been concerned whether we are not often irradiating a normal renal fossa following the apparently complete excision of a relatively small and localized lesion. If any prophylactic therapy should be used, it would appear more logical to attack possible early metastases to the lungs with an intravenous chemotherapeutic agent such as nitrogen mustard.[9, 38, 70]

Recent studies[1, 35] indicate that in the hands of many surgeons there is a slight increase in the survival rate of patients who have received both preoperative and postoperative roentgen therapy, although it is not of sufficient degree to be statistically significant.

A therapeutic regimen advocated by some authorities[1, 50] is to evaluate each tumor individually. In those patients whose tumors are large and presumably malignant and probably inoperable, preoperative roentgen therapy over a one- to two-week period in order to shrink its size is advised. During this period hemic and nutritional deficiencies can be corrected and the child acclimatized to the hospital. Radical nephrectomy under endotracheal anesthesia using a transperitoneal approach is then performed. Roentgen therapy is started immediately after operation as recommended by Gross and Neuhauser.[31]

At St. Christopher's Hospital for Children therapy consists in early radical nephrectomy, as advocated by Ladd and Gross,[43] followed immediately by postoperative roentgen therapy in the conventional manner. We are watching with interest the attempts of others to improve the survival rate by the addition of preoperative roentgen therapy and chemotherapeutic agents such as nitrogen mustard. We are not yet convinced of their value, because no large series of cases has been reported using these adjunctive methods of therapy.

Prognosis

Most collected series of cases of nephroblastoma assume a cure to be equivalent to a two-year survival of the patient. The 2-year survival rate of all patients summarized in recent reports varies from 10.4 per cent,[63] 17.3 per cent,[35] 21.5 per cent,[18] to 47.3 per cent.[31]

In 1955 Collins et al.[17] proposed the prognostic criterion of a "period of risk" following therapy which has proved to be almost infallible. They postulate that the growth rate of cancer before diagnosis may be compared with the growth of a recurrence before its recognition, and that the rate of growth of a metastasis is the same as that of the primary neoplasm. A child's tumor could not have been growing for longer than nine months (gestation period) plus the child's age at the time of its discovery. Based on these criteria, recurrences should become apparent in an equal number of months following therapy. This is the patient's "period of risk" and provides a basis for individual prognosis. After analyzing 340 case reports in which adequate information for evaluation was available, Collins[18] has found only 2 patients in whom recurrence or metastasis occurred after the patient's period of risk had expired. We have found two additional proved patients,[13, 46] and a third presumptive one[58] in whom no histologic proof is mentioned. The application of this "period of risk" principle to each patient provides the most accurate evaluation of their prognosis which is available to date.

OTHER MALIGNANT RENAL TUMORS

HYPERNEPHROMA

Hypernephroma, or clear cell renal carcinoma or Grawitz's tumor, occurs rarely in infants and children. Some authors[12, 43, 53] believe that adrenal tissue in the kidney may be responsible for the hypernephroma; others believe that it may arise from renal tubular epithelium.[2, 28]

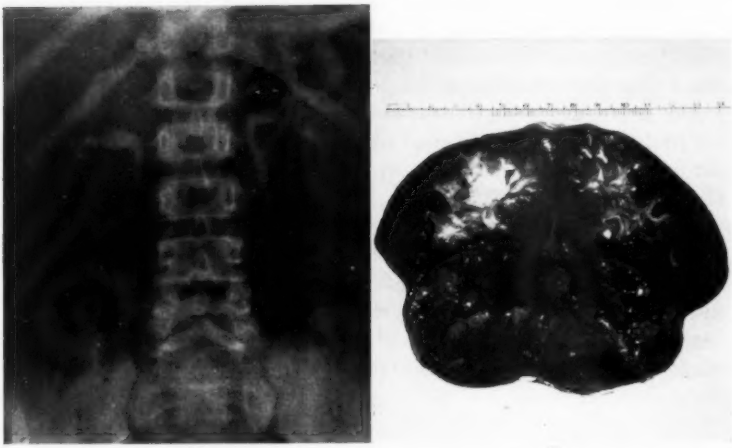
This tumor is a solid neoplasm arising within the kidney. It is composed of cells with clear, foamy cytoplasm resembling those of adrenal cortex which are not infrequently found in otherwise normal kidneys. The tumor has been reported occurring in a six-months old infant by Scotti.[65] The Children's Hospital in Boston reports that they have encountered no such neoplasm in 30 years.[30] At St. Christopher's Hospital for Children two patients with hypernephroma have been seen. One was an 8-year-old boy who died 6 months after operation with metastasis, and the other patient was an 11-year-old girl who is living and well 6 years and 2 months after operation.

In the reported cases the following *clinical manifestations* were noted. The most frequently presenting complaints were hematuria, gross and microscopic; then abdominal pain and a palpable mass.

Intravenous urogram (Fig. 55) shows an intrarenal space-taking lesion. Calcification occurs in 5 to 10 per cent of these tumors.[16] This calcification may be central or peripheral.

Nephrectomy is the *treatment* of choice. It appears that the tumor is resistant to the usual doses of roentgen therapy. Radiation therapy may be used for palliation of metastatic lesions.

In our review of the English literature[36, 40] we have been able to find 28 cases of hypernephroma in infancy and childhood, including



A B

Fig. 55. A, Intravenous urogram on an 11-year-old girl. This demonstrates distortion of the inferior renal calices on the right and linear calcification in the periphery of the tumor. An asymptomatic abdominal mass had been discovered in the patient's right hypochondrium during a routine physical examination in allergy clinic. B, Surgically excised right kidney from same patient which proved to be a hypernephroma. Patient is living and well 6 years and 2 months after nephrectomy.

2 of our own. In children it occurs roughly twice as often in the male as in the female. The youngest patient was 6 months of age and the oldest 14 years. In this group the survival rate cannot be determined, owing to the short follow-up. These tumors metastasize to the lungs, pleura, liver, bones (skull, vertebrae, long bones, sternum) and intestines.

TUMORS OF THE RENAL PELVIS

These tumors are almost unknown in childhood. Hematuria is the usual initial *manifestation;* a blood clot or tumor may cause renal pain or colic. Intravenous pyelography will usually suggest the correct diagnosis. Riches[57] reports one malignant tumor arising from the renal

pelvis in a child. Campbell,[12] in his review of the literature, reports 1 pelvic epithelioma in a child 3 years of age, one spindle cell sarcoma in a 4-year-old, one large papilloma in a 2-year-old, one malignant papilloma of the pelvis in a 3-year-old, and one 13-year-old child with papillary carcinoma who was well 10 years after nephrectomy. A few sarcomas of the hilus and renal pelvis occurring in infants under two years of age are reviewed by Campbell.[12] The *treatment* is by early nephrectomy.

RETROPERITONEAL EMBRYOMA OF RENAL ANLAGE ORIGIN

These tumors are not attached to the kidney and may occur along the vertebral gutter from the thorax to the pelvis, arising from the kidney anlage. They resemble the kidney nephroblastoma and seem to arise from the remnants of the pronephron or metanephron.[30] Langley[45] summarized six previously reported patients and added one—a nine-year-old child who had pain for one week and was found to have a large right abdominal mass arising from a renal anlage which contained calcification. An intravenous urogram was normal. When excised, only a small piece of renal capsule had to be removed.

Of 88 cases of retroperitoneal tumors reported by Snyder et al.,[68] 84 were malignant; 53.4 per cent of these were Wilms' tumors, and 35.2 per cent were neuroblastomas. The others were fibrosarcoma, rhabdomyosarcoma, myxofibroma, adult teratoma, lipoma, sarcoma, lymphosarcoma and adrenal cortical adenoma.

Neuroblastomas are not discussed in this paper, but these highly malignant tumors must be considered in the differential diagnosis of retroperitoneal tumors.

BENIGN TUMORS OF THE KIDNEY

Hydronephrosis is the most common cause of renal enlargement in infants and children. It usually is caused by a congenital stricture of the ureter or bladder orifices. Other benign tumors of the kidney are rare. They may cause clinical manifestations, but are usually discovered as incidental findings at autopsy. Some of the benign renal tumors which have been described are hemangioma,[12, 61] hamartoma,[72] cysts,[4, 14] polycystic kidney,[4] adenoma,[28] renal fibroma[12] and retroperitoneal lipoma.[34]

The presence of a renal tumor can usually be visualized by the intravenous urogram, but its benignancy or malignancy must be determined by histologic study. If the tumor is localized and satisfactory histologic study (e.g., frozen section) shows it to be benign, partial renal resection may be performed. If there is any doubt about the nature of a renal tumor, nephrectomy should be performed.

SUMMARY

Renal tumors comprise one fifth of the malignant tumors in infancy and childhood. The majority of these are nephroblastoma and usually occur during the first five years of life. Early recognition of these initially asymptomatic tumors requires that physicians regularly perform an adequate abdominal examination on every infant and child. All retroperitoneal tumors should have emergency intravenous urograms performed in order to determine whether the kidney is involved by the tumor and to evaluate the opposite kidney.

Therapy for nephroblastoma consists in early radical nephrectomy and postoperative roentgen therapy. Preoperative roentgen therapy and chemotherapeutic agents are being evaluated in some institutions. There has not been a large enough series of patients treated with these adjunctive methods reported in the literature to date to form a statistically accurate basis for evaluation.

Various benign and other malignant renal tumors have been discussed. These must be considered in the differential diagnosis of an abdominal mass.

The prognosis of patients who have been treated for nephroblastoma can be accurately estimated by using Collins' "period of risk."

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2600 N. Lawrence St.
Philadelphia 33, Pa.

TUMORS OF THE LOWER GENITOURINARY TRACT

JOHN M. CRAIG, M.D.

As in other areas of the body, tumors of the genitourinary tract (for tumors of kidneys, see p. 473) in those below the age of puberty, with the exception of ovarian teratomas, occur in forms which are unusual in adults. Here, too, as elsewhere in the first decade of life, the tumors are more often related to mesenchymal than to parenchymatous structures, and to organogenesis than to disorders of epithelial proliferation and maturation. The overwhelming majority of such tumors fall into two broad categories: (*a*) those arising in the ovary and testes as teratomas or their malignant variants, and (*b*) those arising from the region developed from the primitive genitourinary sinus, namely, those of the cervix, prostate and bladder.

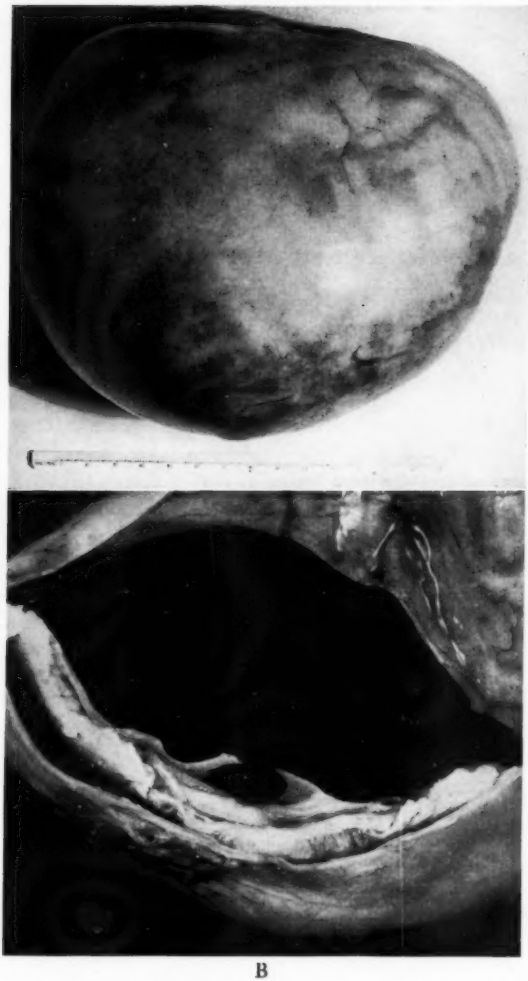
OVARIAN TUMORS

TERATOMA

The most common tumor of all this group is represented by the ovarian teratoma. Adapting the terminology of Rupert Willis,[30] we consider both the dermoid cysts and solid teratomas to fall within this classification, distinguishing only the benign and malignant forms, since all "dermoid cysts" have at least two germ layers represented. Such teratomas comprise from 45 to 80 per cent of all ovarian tumors in the various series related to this age group.[4] Of these, the great majority are benign, none of the 35 seen by us from either surgical or autopsy material falling into the malignant category. The reported malignant varieties have chiefly carcinomatous or chorio-epitheliomatous elements, the metastases arising from these histologic structures. Peritoneal im-

From the Departments of Pathology, the Children's Hospital, and Harvard Medical School, and The Children's Cancer Research Foundation, Boston, Massachusetts.

A



B

Fig. 56. A, A large, smooth-surfaced, benign teratoma of the ovary in a 3-year-old girl. B, Portion of the large cyst from the same specimen. A portion of bone structure is present.

plants of primitive neuroglial or epidermal structures may occur if the tumors undergo rupture.

Such tumors usually replace most of the ovary, and have smooth surfaces, occasionally punctuated by nodules of firmer tissue (Fig. 56). When cyst formation is prominent, they may reach a size to fill the

lower part of the abdomen, yet give rise to few symptoms. On cross section some cyst formation is nearly always present; this may be a predominant feature of those containing a restricted number of embryonic elements such as skin and hair. Then large amounts of sebaceous material and desquamated epithelial cells may fill the lumens of the cysts. In the solid teratomas of the ovary in the infant or child the variety of tissues represented is often much greater. In nearly all such, cartilage, bronchial glands and neuroglial tissue, often with ependymal-lined spaces, are present in varying proportions, while pancreatic elements, smooth muscle and adult fat deposits are more rarely seen. The

Fig. 57. A hemorrhagic, infarcted teratoma from a 10-year-old girl who presented with abdominal pain.

tissue which is most difficult to predict in its behavior is the primitive neuroglial element, which often has the appearance of a neuroblastoma, yet from our experience and that of the literature does not behave as a metastasizing element. A significant percentage of such teratomas, especially of the cystic variety in infants and children, are infarcted as a result of a twisted ovarian pedicle, and then will have massive hemorrhage into the cysts and necrosis of the solid portions of the tumor (Fig. 57). It would appear that this is a more common occurrence than is seen in adults. During reproductive life about 25 per cent of the ovarian teratomas are bilateral,[20] and such bilateral tumors may occur in childhood also, though only one instance of this is known to us; but since these are slowly growing neoplasms, a later appearance

of a second teratoma may be seen in a higher proportion of such patients.

As judged by our experience, the *incidence* of ovarian teratomas would appear to increase just before the onset of puberty, though cases have been seen in the first year of life; again the slow growth rate of such tumors may give a deceptive indication of their inception, yet it must be pointed out that their natural history is quite distinct from that of sacrococcygeal teratomas, which for the most part are recognizable at birth.

The *symptoms* which usually bring children with such tumors to the attention of the physician are abdominal pain, often severe in those with infarcted tumors, an abdominal fullness or the palpation of a mass by the child or parent. In a significant proportion of cases the abdominal pain is recurrent, suggesting repeated partial torsion of the ovarian pedicle. In an occasional case routine x-ray films of the abdomen taken for other reasons may reveal calcific areas in the lower part of the abdomen. In a few reported instances the signs of isosexual precocity in a prepuberal child may initiate investigative procedures, leading to a diagnosis of a teratoma bearing malignant chorio-epitheliomatous elements.

It has been pointed out[22] that only in a child can such chorio-epitheliomatous elements be proved to have their origin in the ovary and not to result from malignant degeneration of a hydatidiform mole with metastasis from the uterus, and indeed the majority of such cases are reported in children. Oliver and Horne[22] found nine cases of chorio-epithelioma below the age of puberty, of which four produced symptoms of precocious sexual development.

The *diagnosis* is usually established only after exploratory laparotomy, because of the presence of pain or a palpable abdominal or pelvic mass, though occasionally the presence of radio-dense bone or tooth structures can be identified, or distortion of the pattern of an intravenous pyelogram may be recognized.

The *therapy* of such tumors is of course complete removal, with the remaining ovarian segments on the affected side; since peritoneal implants have been known to occur, aspiration and partial removal would appear contraindicated. The extraordinary gains in the practice of abdominal surgery are of historical interest and are well illustrated by the report to the Johns Hopkins Hospital Medical Society of 1905,[28] where Kelly's mortality figures of 21 and 33 per cent for dermoid cysts and teratomas in children of that period were reported.

The *life expectancy* of such patients bearing teratomas is hard to assess, since most series in children do not concern themselves with the more benign neoplasms, and the more primitive malignant ones are uncommon, but it may be said that the choriocarcinoma arising in

a teratoma is highly lethal, none of the 12 patients surveyed by Oliver[22] surviving more than 8 months after operation.

FOLLICULAR CYSTS

Relatively more frequently than in adult life, follicular cysts become of such size as to be detectable by palpation or by enlargement of the abdomen in a small child. The great majority of these are nonfunctional, and indeed it is believed by some[23] that in most instances in which follicular cysts are associated with sexual precocity, this is of the constitutional idiopathic type not associated with any functional abnormality in the ovary. However this may be, there are several reports in the literature in which signs of sexual precocity as well as estrogen excretion regressed after removal of a follicular cyst of moderate to large size.[5, 12, 16] Like the teratomas, these cysts may become twisted on their pedicle, five of seven in one series,[4] a finding apparently more common in infants and children as a result of the narrow base of the ovarian ligament, but particularly of the decreased collagen content present which allows greater stretching of the pedicle. Pain, nausea and vomiting may then be the predominant symptoms.

The "simple cysts" of the ovary would appear usually to be follicular cysts in which the special lining epithelium had disappeared. Grossly, all these cysts, when easily palpable, have but one or two large cavities and very thin walls, and contain a thin, clear watery fluid. Microscopically, a portion of ovarian stroma may be recognized on the surface and near the ovarian ligament; a few primordial ova may be found. The cyst lining consists of rounded granulosa cells with, rarely, changes of luteinization. In other instances multiple smaller cysts may be present; such ovaries rarely reach the large size of the single cavity variety. The latter variety are often bilateral, but fortunately the former are rarely so.

Near and after the onset of puberty, continued bleeding into a corpus luteum or into a theca lutein cyst may reach a palpable size.

Removal of such cysts, when single and large, is the usual procedure, but if the cysts are bilateral and so large as to replace most of the ovarian structures, aspiration followed by resection of the majority of the wall will be necessary to preserve ovarian function. If there is any doubt about the kind of cyst because of the characteristic of the cyst fluid, a frozen section of a portion of the wall should be a guide to the necessity of removing the whole ovary (Fig. 58). Fortunately cystadenomas and pseudomucinous cysts are distinctly rare before puberty, as we have seen by a single unilateral example, so that the danger of spread from peritoneal contamination should be minimal (Fig. 59). When small multiple cysts are present, aspiration of the

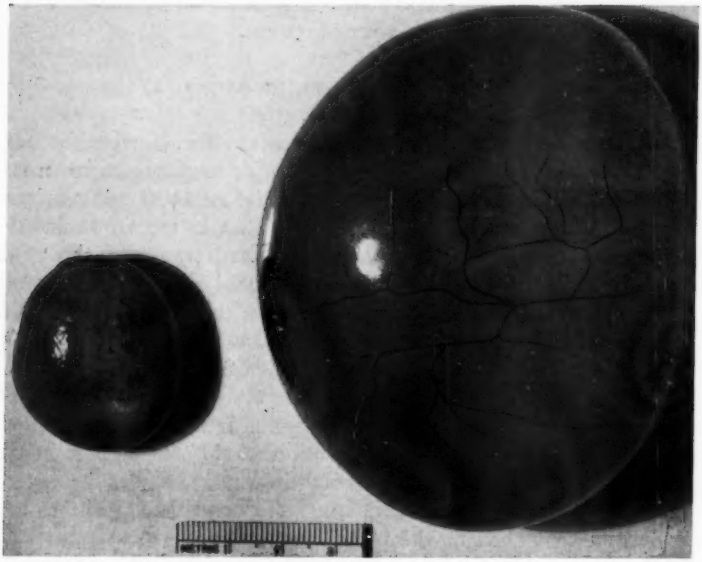


Fig. 58. Large bilateral cysts of the ovary from a newborn infant who presented with an abdominal mass.

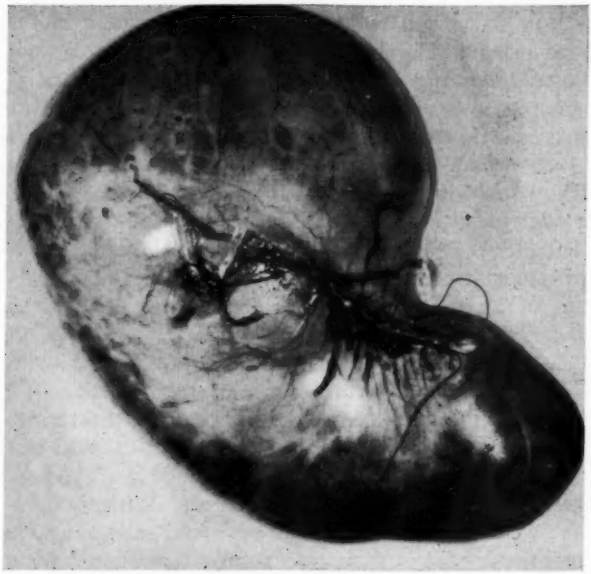


Fig. 59. A pseudomucinous cystadenoma from an 11-year-old girl, having smooth-surfaced walls.

largest should suffice. After puberty the pseudomucinous and cystadenomatous forms of ovarian tumor become more common, and large cysts must be treated by removal without aspiration.

GRANULOSA CELL TUMOR

Perhaps the most interesting of the solid ovarian tumors is the granulosa cell tumor because of its active hormonal production. Yet of all the causes of precocious puberty, those arising from primary increased ovarian function occupy not more than 10 per cent.[23] The granulosa cell-theca cell groups of tumors are the most frequent of the functioning ovarian tumors, comprising about 80 per cent of this group. These tumors only rarely appear in a pure unicellular form; most are mixtures of the rounded, clear granulosa cells having abundant cytoplasm, arising from atretic follicles, and the spindle-shaped lipid-containing theca cells from the ovarian stroma.[15, 27]

Because of the relation of the pure thecomas to the cortical stroma hyperplasia seen in women near the menopause, a condition not seen in infants or children, such pure thecomas are rarely seen in children.[6] Such theca-granulosa cell tumors may give rise to secondary hormonal effects as early as five months after birth.[7] Such tumors are largely solid, but may have small cystic areas within them. Microscopically, they are of some interest because of the presence of fine lipid droplets in the theca cells and the variable presence of alkaline phosphatase activity in these elements. The granulosa cells are mixed intimately with the theca cells in small clumps. Mitotic figures are not common. Areas of degeneration may be frequently encountered. In pure granulosa cell tumors, sheets of round cells are seen, occasionally forming the classic rosettes.

Clinically, the presence of an enlarging mass in the abdomen or pelvis of a prepuberal girl showing hypertrophy of the labia, breast or nipple development, and the presence of vaginal bleeding are diagnostic of a functioning ovarian neoplasm. In all cases when precocious puberty was a symptom, the tumor has been large enough to be made out on abdominal or rectal examination. There may be an advance in height as well as in the bone age. The breasts may give subjective feelings of fullness, tenseness or tingling, and increased pigmentation of the areola may be found. The vaginal bleeding is nonovulatory, so that no secretory phase of the endometrium takes place. Because of this, as is common in adults with such tumors, hyperplasia of the endometrium may be present. The vaginal smear, of course, will be cornified. Pubic hair may appear, suggesting that estrogen secretion may lead to secondary secretion of adrenal androgens.[29] The excretory levels of the

estrogens will be high, and in some an increase in follicle-stimulating hormone may rarely be present.

Surgical removal is, of course, the indicated *treatment*, but it would appear that exploratory laparotomy in cases of isosexual female precocious puberty is not justified in the absence of a palpable pelvic or abdominal tumor. Removal of the tumor may, of course, result in withdrawal bleeding a few days after the operation.

The *prognosis*, particularly of unruptured, intact ovarian masses made up of granulosa-theca cell tumors, is excellent, for in children from the literature surveyed by Pedowitz,[23] only 6 of 96, of whom half were followed up a year or more, succumbed to their disease. Some of the reported "sarcomas of the ovary" undoubtedly were such tumors, but the most common finding by far is that the granulosa cell component is the malignant one, even in the mixed granulosa-theca cell tumors, and metastases from pure thecomas are almost unknown. Granulosa cell tumors may recur in the opposite ovary as long as 30 years after removal of the first ovary, though in such a case it would be difficult to prove that they were derived from one another. Ordinarily the contrary ovary will remain infantile without stimulation.

DYSGERMINOMA

The dysgerminoma is a rare tumor, being about one third as frequent as a granulosa cell tumor in all age groups. This is primarily, however, a tumor of young adults with an average age of 20, but half of the cases may be found in the second decade of life. Only 14 cases had been described up until 1948 in children,[18] and of these 9 occurred before puberty. These tumors may be regarded as having origin in the germ cells and proliferating chiefly at that level of differentiation. Occasionally chorio-epitheliomatous elements may be present just as similar elements may appear in the counterpart in males,[19] the seminoma. In such cases, signs of precocious puberty may be present, and examination of the urine will yield positive tests for follicle-stimulating hormone and estrogens. Pure dysgerminomas are believed not to give rise to gonadotropic hormone, and a positive test would indicate the presence of chorio-epitheliomatous elements. A certain proportion of cases occur in female pseudohermaphrodites with hypoplastic genitalia. A study of the genetic sex chromatin pattern might yield interesting results, in view of the often-suggested relationships between cryptorchid testes and the development of seminomas in the male.

Except in the unusual instance of precocious sexual development or hypogonadism in an adolescent female, the usual *symptoms* are a painless enlarging mass in the pelvis or lower part of the abdomen. The mass may reach large size before presentation for treatment.

Such tumors are irregular in outline and often bosselated or gyriform on the external surface. Not infrequently they are accompanied by ascites. Microscopically, they consist of sheets and nests of large tumor cells with much nuclear material and scant cytoplasm; mixed in among these large cells are much smaller cells having many of the staining characteristics of lymphocytes. Those containing chorio-epitheliomatous elements have primitive anaplastic trophoblastic tissue as well. Stromal components, as fibrous tissue septa, may be present.

Surgical removal alone may suffice if there is no adherence to or invasion of the capsule. With local spread, removal of the uterus, the opposite ovaries and the iliac nodes, followed by radiation to the pelvis, should be carried out, since such tumors are radiosensitive. A high proportion of such tumors, about one third, recur or subsequently develop in the opposite ovary.[18] But unless gross involvement of the other ovary or spread beyond the primary site is found, removal of the opposite ovary in a child or prepuberal girl would seem contraindicated. The level of gonadotropic hormone may fall promptly after operation, but its secondary effects on the remaining gonad may give a positive estrogen response for a few months after operation.

ARRHENOBLASTOMA

The masculinizing tumor of the ovary, the arrhenoblastoma, has not been seen in prepuberal girls, the youngest one mentioned in the literature being 14 years old.[16] Others in which the history of amenorrhea goes back to that age have also been reported.[13] Of 10 patients from the literature under the age of 20 with such tumors, all were puberal. Because of the virilizing effect of the tumors, amenorrhea, hirsutism, masculine habitus, low voice and breast atrophy were accompanying symptoms to the invariably present one of a palpable pelvic tumor. The 17-ketosteroid excretion was elevated in the cases in which it was determined.

These virilizing tumors vary from the tubular adenoma of Pick, which has clear cells in well defined tubular structures, to the more anaplastic tumors with irregularly defined clumps of clear cells and much undifferentiated sarcomatous elements with a considerable collagenous fibrous element.

Surgical excision is the proper treatment, but because of slow growth and lack of alarming symptoms, at least half of the 10 cases noted above were soon shown to be malignant in their behavior by the presence of metastases. In the benign ones, after operation, menses may recommence, the hirsutism disappear and the virilism diminish with return of 17-ketosteroid levels to normal. Spread by peritoneal implantation is most common in the malignant variety.

BRENNER TUMORS

Brenner tumors of the ovary are even less commonly encountered, being primarily a neoplasm of old age. One in a child aged 6 has been mentioned by Jondahl,[10] but in Bland's[3] survey of 35 Brenner tumors from the literature none were present even in the puberal age group. These are benign tumors of epithelial nature, taking their origin from Walthard nests.

Unlike the ovary in adults, the ovary of infants and children does not often harbor a metastatic neoplasm; this is probably a direct result of the infrequency of epithelial tumors of the gastrointestinal tract in early life. The one exception are the tumors of lymphomatous origin. These may occasionally spread to that organ and so form a palpable mass, though usually not a presenting sign of the original disease. In leukemic patients beyond the first four or five years of life, infiltrates are almost invariably found in the ovary, but only when associated with significant hemorrhage do they often form palpable masses.

TESTICULAR TUMORS

EMBRYONAL CARCINOMA

Turning to the testicular tumors, the most frequent one encountered in infants and children is the embryonal carcinoma. In our experience this has occurred as frequently as all the other types together, six having been seen in material of the pathology department. Nearly all of these have occurred in children under two years of age, and may be present at birth.[17] These tumors, if seen before invasion of the tunica, are sharply circumscribed, soft and gelatinous in consistency, bulging above the testicular surface on cutting. Microscopically, the chief element is a large, irregularly shaped cell, with a clear cytoplasm which displays a definite affinity for alignment along a basement membrane and an amazing degree of polarity of its basally placed large nucleus. These cells arrange themselves in irregular papillae and acini. The tumors have a fairly prominent and edematous loose connective tissue stroma.

Clinically, these tumors present with simple enlargement of the testis, which is usually not painful, but is discovered by the mother while bathing the child or during a routine physical examination. The affected testicle may reach a size three to four times that of the opposite testis. Growth may occur rapidly, doubling in size over a few weeks' time. There may be a transmitted bluish color through the scrotal skin. Many of these tumors have been mistaken for hydroceles, but the firmness of the testis and its failure to transmit light should leave no doubt about its true nature. In some instances palpable inguinal nodes, a pelvic mass or the presence of metastatic nodules in the chest indicates spread of the tumor.

The proper surgical *treatment*, once the diagnosis has been established, is to explore the cord structures and palpate the iliac chain of nodes with preparation for excision of the iliac nodes through an extension of the original incision, and with removal of all the cord structures and tunica with the involved testis. If histologic involvement of the node structures is found pathologically, radiation treatment should be given to the lower part of the abdomen and pelvis; though such treatment has not been shown to have the clear-cut therapeutic value that radiation gives in seminomas of the testis, one case in which tissues were seen in consultation had disappearance of an iliac mass after radiation.

The *prognosis* in such tumors is serious, but by no means hopeless. In a series of 4 at the Mayo Clinic,[24] all succumbed, but of 8 treated by Gross,[8] 5 are living and well 6 months to 10 years later. None of the living patients had evidence of spread outside the testis at the time of the original operation, and all who died did have such spread. One child described in the literature went six months between the discovery of the testicular enlargement and operation, yet is still well five years later.[25]

TERATOMAS

The teratomas in infants and children also tend to appear at or shortly after birth; 20 of Julien's[11] 32, 3 of 9 teratomas in Ruscke's[25] series, and 2 of 3 of our own teratomas appeared in the first few weeks of life. In most series these appear in the first two most frequently found testicular tumors.

Like the embryonal carcinomas, these tumors appear as asymptomatic unilateral enlargements of the testis, discovered during bathing or physical examination. Growth of the tumor may not be as rapid as in the embryonal carcinoma group.

The teratomas vary, as in the ovary, from ones with a great variety of mature and immature embryonic elements, the dermoids at one end of the scale and the solid tumors containing primitive glial or neuroblastic tissue as the most primitive element (Fig. 60) at the other. None of the 7 reviewed by Mostofi,[17] of 9 by Ruscke[25] were considered to be malignant, while one each seen by Phelan,[24] Julien[11] (of 32) and ourselves were considered histologically malignant. But two of these are known to have developed metastases. This is a decided contrast to the teratomatous tumors of the adult testis, which are often highly malignant. This change is related to the presence in them of malignant degeneration in the epithelial structures of teratocarcinomatous or chorioepitheliomatous elements; the latter have not been reported in infants and children.

Surgical *therapy* is indicated here, and since the diagnosis really can-

not be established until the orchidectomy has been completed, a preliminary examination of the cord structures must be performed. The use of radiation would not be justified postoperatively unless definite local spread or node metastases were recognized at operation.

The *prognosis*, as can be judged from the rarity of the tumor, is excellent, only 2 of 52 having any metastasis.

It is a common understanding among pathologists that seminomas of the testis are rare in infants and children, though such tumors form

Fig. 60. A histologically malignant teratoma of the testis from a 6-weeks-old boy. The tumor is well circumscribed, but soft and gelatinous.

the largest single group in young adults. At least two have been reported in the literature, however, in this age group.[24]

INTERSTITIAL CELL TUMORS

The next group of tumors to be considered arising from the testis are the interstitial cell tumors. Such tumors are functionally active and induce precocious puberty. The majority of the 18 cases in the literature occurred in children 2 to 6 years of age.[29] All were benign in behavior with no evidence of invasion or metastasis.

Such tumors have measured up to 12 cm. in diameter and are made of sheets of large, polygonal, eosinophilic, granular and often lipid-bearing cells with small nuclei; they usually are larger than, but cytologically do not greatly differ from, their nontumorous counterpart in the interstitial cell of the adult testis. Mitotic figures are rarely seen. In children having such a tumor the remainder of the interstitial cells have a form consistent with their age, though there may be slight development of the testicular tubules.

Clinically, the evidence of sexual precocity may antedate recognition of the offending tumor. Virilism with maturation of bone structure, hypertension, sodium retention, and excess excretion of the 17-ketosteroids are seen in these children. Characteristically and importantly, the tumor occurs in only one testis. A number of cases of bilateral enlargement of the testis due to proliferation of the interstitial cells in cases of primary adrenal cortical hyperplasia have been misinterpreted[26] as arising from testicular tumors. These children, too, because of the excess androgen production of the abnormal adrenals, will have virilism, advanced bone maturation and occasional hypertension. Their testes, usually later in life than those with a primary tumor, will both contain tumor masses and may be irregularly nodular.

Wilkins[29] suggests that cortisone administration may result in shrinkage of such tumor masses, which would not occur in the primary interstitial cell tumor. A prompt response in urine 17-ketosteroid levels should follow removal of the primary tumor, a response which would not be expected even if both testes of the adrenal-genital case were removed, because of the large amounts of hormone derived from the adrenals.

Removal of the testis without iliac dissection would seem adequate *therapy* for such tumors, since none of them have been reported to have metastases. There is often prompt regression, though not complete, of the virilism and hypertension.

METASTATIC TUMORS

Metastatic tumors may involve the testis, probably more frequently in the young than in adults, and in a proportion of these the metastatic

Fig. 61. A malignant lymphoma involving the testis of a 12-year-old boy.

focus may appear as the leading sign in the malignant process arising elsewhere. This appears to be particularly true of the tumors of the hematopoietic tissues. We have had three such instances (Fig. 61), two with lymphosarcoma and one with reticulum cell sarcoma. Most such cases have other evidence of disseminated disease, particularly the presence of abdominal or pelvic masses. The frequency with which lymphomas or acute leukemias may involve the testis is seen in the figures given by Andersen[1] of 11 cases of lymphomatous involvement and 12 of leukemic involvement of the testis in the series at the Babies Hospital, presumably most of them at autopsy.

TUMORS OF TUNICA

Tumors of the tunica of the testis are also seen in large series of tumors of the male genitals in children. Rhabdomyosarcoma is one of the most frequent, and in the absence of operation or postmortem examination it may be difficult to ascertain whether these really originate in the cord structures or are metastatic from primary tumor masses in the pelvis; examples of both have been recognized. Many such tumors are originally diagnosed as inguinal hernias or hydroceles, and it is not until exploration that the true nature of the lesion is discovered. Fibrosarcomas have also been recognized as primary tumors in the tunics of the testis.

Metastatic tumors in the tunics of the testis may give rise clinically to a presenting scrotal mass: these have been primarily those arising in embryoma of the kidney or Wilms' tumors; more often these metastases take place late in the disease. If such tumor tissue is seen in an apparent primary tumor in the cord structures, a search for the primary tumor by pyelogram should be mandatory.

Occasionally non-neoplastic processes have been misdiagnosed as primary testicular tumors. One of these in our experience was a torsion of the testicle with massive hematoma, which gradually increased in size over a period of weeks, with no history of previous pain or trauma, incredible as this may seem. Here removal of the testis was carried out. Another source of error may be the presence in hydrocele sacs of regions of fibrin deposit and fibroblastic, proliferative organization when trauma has been known to occur. Such local proliferations may give rise to small, macrosopic, elevated masses within the tunica, with active proliferation of immature cells suggesting fibrosarcoma.

TUMORS OF BLADDER, PROSTATE, CERVIX AND VAGINA

The group of tumors arising in the bladder, the prostate, the cervix and vagina all have the same histology and much the same behavior patterns

once local spread has occurred. These are the mixed mesodermal *sarcomas*. They are also called rhabdomyosarcomas because of the usually easily demonstrable cells with longitudinal and cross striations in them. Those which have their origin near the mucous surface of a hollow viscus, such as the bladder, cervix or vagina, form pedunculated polypoid masses, often showing rapid growth and swelling; because of their resemblance to bunches of grapes, these are called "*sarcoma botryoides*." Some 30 such tumors have been found in the files of the pathology department at The Children's Hospital. Of those arising in the submucosa of the bladder, the males outnumber the females two to one, but the total number found in the pelvic area from bladder, prostate or vagina, or from an indeterminate pelvic source in late cases, is about equal in males and females.

In the most freely growing areas in the bladder or vagina the tumors achieve their most distinctive form. Here they form polypoid, translucent masses attached by a broad base, and invade the underlying tissue. Microscopically, while the tumor cells may be closely compacted in certain areas, in most zones the tumor cells are set in a loose edematous and acollagenous stroma. The tumor cells are often small and fairly regular with the characteristic strap or tadpole cells containing long acidophilic tails with longitudinal and cross striations interspersed among more primitive cells, a few being fibroblasts. The overlying epithelium is thinned and stretched, and here cells may be more compactly placed. Where constricted by the surrounding tissue, the tumor cells grow more closely together. This is also seen in the tumors arising from the prostate, where large nodular masses surround the prostate, base of the bladder and ureters, and compress the rectum. Such tumors rarely metastasize to local lymph nodes, but may spread locally to fill nearly all the lower part of the abdomen. Metastases, when they do occur, are chiefly to the lungs, but widespread bone, skull and marrow metastases have been seen.

Those in the bladder present most frequently with dysuria, bladder neck obstruction with dribbling and bladder distention, hematuria or pyuria (Fig. 62). These *symptoms*, occurring as they do in young children under five, may not be noticed by the parent until late. The late symptoms include renal insufficiency due to ureteral obstruction and pyelonephritis.

The next most common site of origin is the cervix or vagina. These too are seen chiefly in young infants, and they have been seen in the newborn (Fig. 63) (two of these were operated on in this hospital and have been reported by Ober[2]). The presence of a bloody or mucoid vaginal discharge has been noted frequently at onset, or a tumor has been seen at the vaginal orifice. Since at least one benign tumor has been reported arising from the cervix of a three-year-old girl,[9] and we

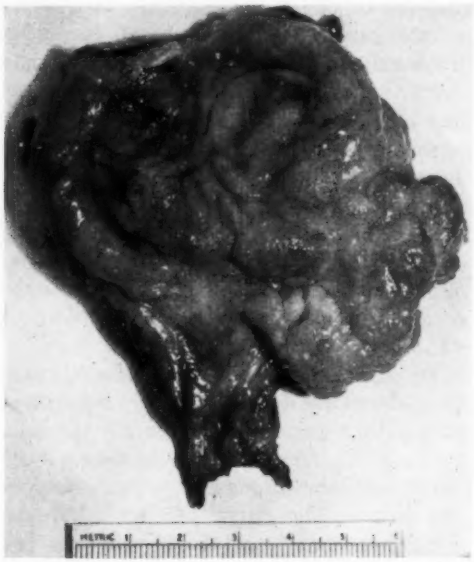


Fig. 62. A mixed mesodermal sarcoma of the bladder (sarcoma botryoides) from a 1 7/12-year-old girl, who is well 1 year after cystectomy.

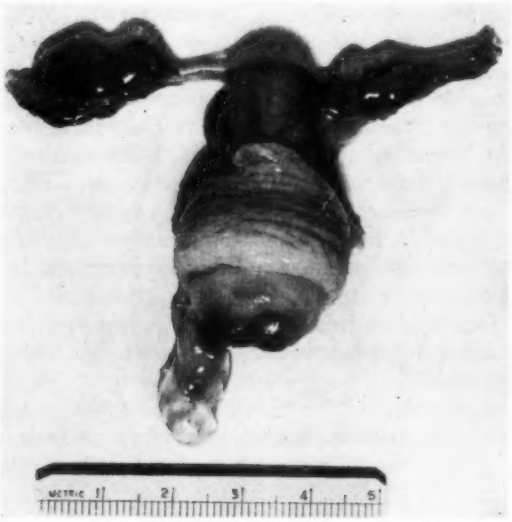


Fig. 63. A mixed mesodermal sarcoma of the cervix in a newborn girl, discovered at autopsy.

have mistakenly made a gross diagnosis at autopsy on a cervical polyp in a newborn dying of another disease, a biopsy diagnosis on paraffin-sectioned material is mandatory before radical surgical therapy is instituted.

The remainder of the cases unfortunately arise deep in the prostate or cervical tissues, and so give no early sign of their presence. These are not discovered until distortion of the rectal, ureteral or urethral passages has occurred and resulting obstruction gives notice of their presence. Occasionally, only when the respiratory distress secondary to extensive pulmonary metastases calls the child's condition to attention are the tumors found.

Diagnosis of those which lie free in the bladder lumen may be established after cystogram, cystoscopy and biopsy. Those of the cervix and vagina are usually readily accessible to direct attack by biopsy, while those arising deep in the pelvis usually require an exploratory laparotomy.

The proper *surgical attack* appears at present to be complete cystectomy for the tumors arising in the bladder submucosa, with transplantation of the ureters into the rectosigmoid. Those arising in the cervix or vagina have of recent years, except when extension demands more widespread organ removal, had resection of the uterus and vagina at one stage, leaving only the ovaries. In the third group, arising in the prostate or deep cervical tissues, none have been suitable for operative attack, owing to the massive local extension of the tumor or to distant metastases. Radiation therapy appears to have little or no influence on such tumors.

The *prognosis* in such tumors was unusually poor in the past, owing to late diagnosis and inadequate surgical therapy. It would appear that when surgical attack is prompt and vigorous, particularly in those tumors giving rise to surface growths in the bladder, cervix and vagina, an appreciable number of children can be saved. One vaginal tumor (Fig. 64) has now gone eight years after uterine and vaginal resection without recurrence, while two newborn infants have gone three years from their vaginal and uterine removal without reappearance of the tumor. A fourth child, who had a cystectomy, has gone one year without evidence of recurrence.

Carcinoma of the squamous variety has been reported in the literature in five cases in infants and children, with massive hemorrhage and urethral obstruction reported. These are grade I papillary carcinomas.[14]

Tumors of the external genitalia are rare in infants and children, but include a rhabdomyosarcoma of the penis and a benign granular cell myoblastoma of the labia majora.[2]

Fig. 64. A mixed mesodermal sarcoma of the vagina from a 1 1/12-year-old girl, who is well 8 years after removal of the uterus and vagina.

SUMMARY

In infants and young children the majority of ovarian tumors are benign, particularly when unassociated with precocious sexual development. In the testis the frequency of malignancy is statistically much higher, particularly in young infants. The tumors of the bladder, vagina and prostate in this age group are almost always malignant; prompt and vigorous surgical therapy must be instituted if life is to be preserved in the latter two groups.

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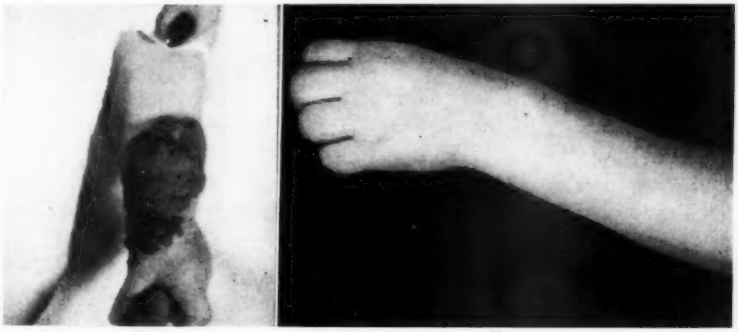
300 Longwood Avenue
Boston 15, Mass.

MANAGEMENT OF HEMANGIOMAS IN INFANTS

ISADORE LAMPE, M.D.

HOWARD B. LATOURETTE, M.D.

Diversity of opinion as to the management of hemangiomas in infants has existed for at least a half century. Surgical excision, application of carbon dioxide snow, beta-ray radium irradiation, gamma-ray radium treatment, roentgen-ray treatment, radon seed application and injection of sclerosing solution all have had their enthusiastic advocates.[1, 6, 7, 15, 20] Some workers advise immediate therapy; others recommend postponing active intervention for variable periods. Alarmed by the presence of an enlarging disfiguring lesion, parents become understandably confused and distraught by the differing advices pre-



A B

Fig. 65. A, Hemangioma at age 5 months. Present at birth, this lesion doubled in size by 5 months of age. Only the upper half of the lesion was treated with small doses of x-ray at ages 5 and 7 months; the portion over the wrist and hand was not treated. *B*, At age 4½ years. The site was flat with slight, irregular residual redness. Treated and untreated areas regressed equally well.

From the Alice Crocker Lloyd Radiation Therapy Center, University of Michigan Medical Center, Ann Arbor.

sented to them. This situation is particularly regrettable since in the last 20 years much progress has been made in our knowledge of the natural history of the type of hemangioma which is overwhelmingly the predominant offender in infancy.

This lesion, which in this paper will be called the involuting type, has been variously designated: strawberry nevus, capillary hemangioma, hypertrophic hemangioma, cavernous hemangioma, vascular nevus, as well as other terms. Involving the skin and/or the subcutaneous tissues, it presents as a slightly elevated, bright red lesion (Fig. 65) to a massive, tense red tumor (Figs. 66, 67, 68) and may be associated with

A B

Fig. 66. *A*, Hemangioma at age 3 months. A small hemangioma, present at birth, enlarged rapidly, causing the referring physician to suspect a malignant tumor. Only portions of the lesion were treated with small doses of x-ray at 3 and 5 months of age. Ulceration and 1 episode of bleeding requiring a compression bandage occurred at 3½ months of age. *B*, At age 31 months. Evidence of regression was noted at age 7 months and continued steadily to the time the patient was last seen, at age 32 months.

subcutaneous tumefaction (Fig. 69), or it may occur solely as a subcutaneous mass which may give a slight blue discoloration to the overlying skin (Fig. 70). Appearance alone, however, does not always suffice to characterize the kind of hemangioma pertinent to this discussion, and differentiation may require a knowledge of the course of the lesion during the first few months of life.

COURSE

The natural history of the involuting type was first described in complete form by Lister[13] in 1938. His observations, made on 92 hemangiomas in 76 infants in whom all forms of treatment were withheld, may be summarized as follows: These lesions enlarge more or less rapidly during the first few months after their appearance. Growth never continues beyond one year of age; often it ceases between the sixth and eighth months. After this, regression sets in. By the fifth year all trace of color usually is gone. In the larger lesions more

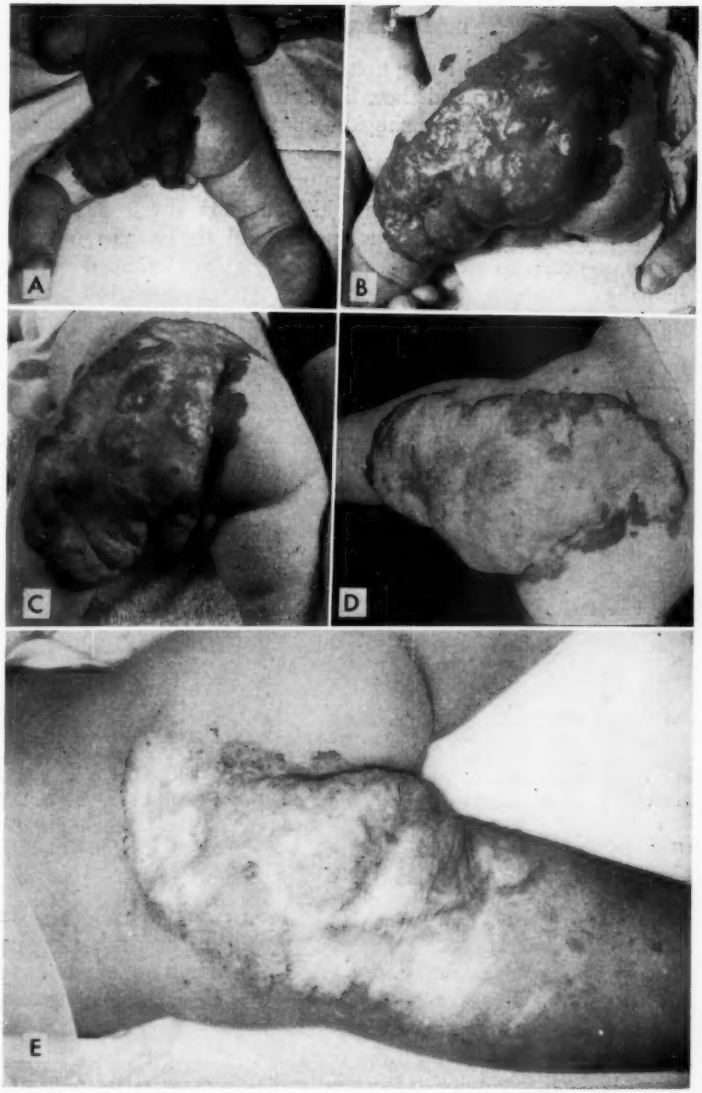


Fig. 67. *A*, Hemangioma at age 5 weeks. A large hemangioma of the buttocks, genitalia and upper thigh was present at birth and enlarged as manifested by increased elevation above skin level. Multiple small hemangiomas were present elsewhere on the body. At 5 weeks ulceration developed along the gluteal crease and spread across the surface. *B*, At age 5 months. The lesion continued to increase in thickness. Careful nursing care, soaks and bakes plus several small doses of x-ray (75 roentgens) to small infected areas resulted in healing of the ulceration. *C*, At age 7 months. The ulceration healed, but the red color persisted, and the lesion was thicker. *D*, At age 13 months. Involution started between 7 and 9 months of age. By 13 months regression was taking place rapidly, as shown by blanching and decreased elevation. *E*, At age 3½ years. Only traces of color and mild thickening remain. Scarring due to previous ulceration is apparent. The lesions elsewhere on the body also were regressing.

time is required for final absorption of redundant skin. Those lesions which persist into adulthood show little growth in early childhood.

It is true that not all hemangiomatous lesions noted in infancy eventually regress spontaneously. Although erythema nuchae (salmon patch, neonatal staining) usually disappears spontaneously, the port-wine mark (nevus flammeus), the spider angioma, the true cavernous lesion with adult type of venous spaces, and the venous racemose aneurysm do not. Also noninvoluting are the group of lesions designated as hemangiomatous varicosities, or diffuse hemangiomatosis, which are often associated with gigantism of the involved part; many or all

A B

Fig. 68. A, Hemangioma at age 7 months. Present at birth, the lesion grew during the first few months. Carbon dioxide snow treatment carried out elsewhere produced partial surface blanching with scarring, but the subcutaneous compartment continued to enlarge. We first saw the patient at age 7 months. The lesion was kept under observation. By age 14 months slight regression was noted; by age 30 months, considerable regression. *B*, At age 7 years. Scarring from carbon dioxide snow treatment was evident.

of this type contain multiple small arteriovenous shunts, and the process is one of progressive extension; a lesion resembling a port-wine stain may be an early manifestation of this disease. The noninvoluting lesions constitute only a small fraction of the hemangiomas observed in infancy. The essential problem for proper management is differentiation of the involuting from the noninvoluting type.

Since 1947, 510 patients with nearly 600 hemangiomas of the involuting type have been seen in the Alice Crocker Lloyd Radiation Therapy Center of the University Hospital. In about 500 lesions the period of observation was sufficiently long to provide insight into the course of the disease under conditions of minimal or no treatment. In a previous report[12] on 471 lesions, cutaneous involvement was noted in 63 per cent, subcutaneous in 15 per cent and both cutaneous and subcutaneous in 22 per cent. The female to male ratio was 2.5:1.

Fig. 69. *A*, Hemangioma at age 5 months. This child was born with a right congenital microphthalmia and hemangioma of the orbit, temple, preauricular region and upper lip which enlarged. The right orbital region was irradiated (100 roentgens a day to a total of 600 roentgens). Rapid and pronounced regression occurred, but by 8 months of age the lesion had enlarged again, almost to its original size. *B*, At age 8 months. Small areas on the upper eyelid and at the outer canthus were irradiated with small doses of x-ray without effect. No further treatment was given, and the situation remained static until some time after 16 months of age, when involution began. *C*, At age 3 years. Regression was pronounced. The right preauricular, never treated, involuted completely; the upper lip lesion, untreated, had regressed partially. The right eye, functionless from birth, was scheduled for removal.

A recorded history of similar lesions in siblings was found in 3 per cent of the cases.

Sixty-one per cent of the lesions were present at birth; 86 per cent were present at birth or appeared within the first month. Early growth was noted in 85 per cent of the cases; in the remainder no information on this point could be obtained. Enlargement in the first few months

Fig. 70. *A*, Subcutaneous hemangioma, present since birth, at age 13 months. This lesion was not treated. *B*, At age 4 years there was complete regression. The process of involution started between 20 and 26 months of age.

of life is of prime importance in identifying those lesions which eventually will involute.

CLINICAL MANIFESTATIONS

The observation of early enlargement is readily made and reported by the parents in most cases. In some instances this information is obtained only by careful interrogation. The lesion may not have increased in area, but may have become thicker, this change escaping the parents' notice. Patchy areas of skin involvement may coalesce; this may be forgotten. In some cases a short period of observation has

verified growth of the lesion (Fig. 71). Not being pediatricians, we almost never see these patients before onset of the lesion. Jacobs[10] and Blackfield[4] report that the earliest manifestations are sharply delineated pale areas which then become red. Within a few weeks the lesion becomes raised and may go on to develop into a large mass.

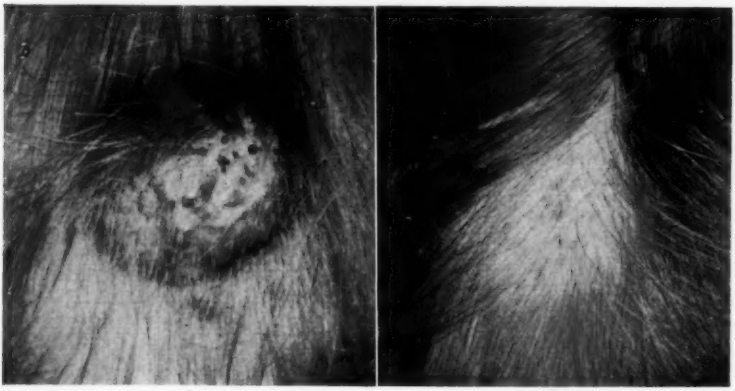
Maximal size is reached within the first year of life. In half of our cases growth ceased before 6 months of age; the remainder attained maximal size between 6 and 12 months of age. An occasional hemangioma enlarges at an alarmingly rapid rate (Fig. 66). The fear of malignancy may lead to drastic therapeutic measures which often

A B

Fig. 71. A, Hemangioma at age 3 weeks. At 2 weeks of age a red area was noted on the upper lip to the right of the midline. *B*, At age 5 months. The hemangioma enlarged steadily to this maximal size.

produce undesirable late sequelae: scarring, radiation damage of soft tissue, decreased bone growth, and so on (Fig. 68). Biopsies of such lesions are often reported as showing highly cellular tissue, possibly sarcomatous, which only adds fuel to the fire.

After growth has ceased a stationary period of varying duration follows before evidence of regression appears. The initial manifestation of regression in a cutaneous lesion will consist in fading of the original brilliant red to a duller red and then to a grayish hue. The alteration appears first in the center and gradually spreads to the periphery. Later a decrease in the tenseness of the overlying skin, often manifested by a slightly wrinkled appearance, develops when the bulk diminishes. Gradually the lesion decreases in thickness. The size of the area involved by the lesion diminishes late or not at all (Fig. 67). The early signs of involution appeared before 6 months of age in 16 per cent



A B

Fig. 72. A, Hemangioma of the scalp at age 6 months. The hemangioma appeared shortly after birth and grew for 3 months. Dry ice treatment given elsewhere at age 2 months produced the blanched area; there was no further treatment. *B*, At age 2½ years. Involution started between 10 and 17 months of age and was essentially complete at 2½ years of age.

A B

Fig. 73. A, Hemangioma at age 8 months. Swelling of the lip was first noted at age 3 weeks and gradually increased in size, involving the vermilion surface and the labial mucosa. No treatment was given. *B*, At age 2 years. Regression started at 11 months of age. At 2 years a slight droop was the only residuum; contour and color of the labial mucosa were normal.

of our cases, between 6 and 12 months in 65 per cent and not until after 1 year of age in the remainder. In most cases, by five years of age the lesion has disappeared or only traces of color remain (Figs. 67, 70, 72–75); this occurs with or without treatment (Fig. 65). In bulky lesions more time may be necessary for adjustment of redundant skin (Fig. 68).

A B

Fig. 74. A, Hemangioma of right upper eyelid at age 8 months. The hemangioma became apparent at age 4 months and enlarged for a short period. The patient was first seen at age 8 months; no treatment was given. B, At age 39 months. Regression began between 14 and 17 months of age. At 39 months only slight thickening remained.

Fig. 75. A, Hemangioma at age 5 months. A small, flat, red area was noted at birth on the left forearm. Ulceration and crusting had been present for 1 month when the patient was seen by us at age 5 months. B, At age 34 months. With soaks and bakes the ulceration gradually healed (no other treatment). Retrogressive change was noted by 8 months of age and continued. Note the residual skin atrophy.

The natural history of this lesion is not in accord with that of a true neoplasm. Willis[21] states that it is a congenital vascular malformation and that the increase in size early in life is not due to cellular proliferation, but "to canalization and establishment of a blood-flow in fresh parts of an already existing malformation."[21] The microscopic picture may be disturbing because poorly canalized vasoformative tissue may appear highly cellular and invasive. Another point of view is advanced by Swerdlow,[17] who believes that the involuting type of hemangioma consists of embryonic vascular endothelial cells which for unknown reasons escape control and continue to proliferate. Mitoses are noted at first, but later disappear. According to this conception, the enlargement of this lesion is due to cellular division and multiplication of non-neoplastic embryonic cells. No satisfactory explanation has been advanced as yet to explain the process of involution.

TREATMENT

Identification of Type of Lesion

Correct identification of the type of lesion is the first step in the management of hemangiomas of infancy. The involuting type must be differentiated from those lesions which will not regress spontaneously. Lesions which enlarge during the first few months of life and cease growing before one year of age will involute. Lesions which do not grow early in life, as a rule will not regress spontaneously, although infrequent exceptions have been seen. Some lesions, present at birth, show no growth until after one or two years of age or later—such lesions do not involute spontaneously. These may be true cavernous hemangiomas of adult venous structure or the type of hemangioma containing arteriovenous shunts. A rare case of the latter variety may grow during the first year of life, but growth continues beyond that time. Port-wine marks and spider angiomas are usually readily differentiated from the involuting type. Some lymphangiomas with red blood cells in their spaces may simulate hemangiomas. The noninvoluting types require treatment for eradication, but it is virtually certain that radiation treatment will obliterate such lesions only at the price of serious radiation damage of normal tissues.

Aim of Treatment

The principal danger in the management of the involuting variety of hemangioma arises not from any feature of the disease, but from overzealous therapeutic measures. Surgical excisions and plastic re-

arrangements often will leave cosmetic blemishes which would not follow conservative management. Overenthusiastic radiation treatment of any kind, though effecting rapid and complete regression, will produce obvious or latent radiation damage of tissue. Years later, skin changes and limitation of bone growth may become apparent. The aim

Fig. 76. *A*, Hemangioma at age 4 months. No history was available in this case. The left upper eyelid and adjacent region were massively involved by an ulcerated infected hemangioma. Conservative treatment for 3 weeks cleared up the infection and reduced the extent of ulceration, but the lesion continued to enlarge. Vision was completely obstructed. With the globe protected, small doses of x-ray were given over 5 days. In 2 weeks the palpebral fissure was partly open. *B*, At age 11½ months. Partial regression had occurred.

of treatment must not be the disappearance of the lesion with the presence of apparently normal tissue at the site several years after treatment, but must be the presence of undamaged normal tissue decades later. The radiation dose which will avoid significant late tissue sequelae, particularly when administered in multiple, small repeated doses over

a period of time, has not been established precisely. Sclerosing agents at times produce slough of tissue with subsequent scarring. Overtreatment with carbon dioxide snow will scar the skin without effecting a subcutaneous component (Fig. 68). The same phenomenon may follow beta-ray irradiation.

As radiologists, we were trained in the belief that all hemangiomas in children must be treated and, of course, that radiation therapy (at first radium, and later roentgen-ray treatment) was the method of choice. Furthermore, we were taught that these lesions were highly radiosensitive. Gradually, on the basis of empiric observation, the amount of radiation used was reduced and the extent of the indications for treatment restricted. With the demonstration to our own satisfaction of the accuracy of Lister's observations, radiation therapy has been abandoned as the basic therapeutic approach in favor of no active treatment of any kind. At present our indications for radiation treatment are few, and they apply infrequently. If vision is totally obscured by massive eyelid involvement, by carefully shielding the eye we have irradiated the lid to open the palpebral fissure (Fig. 76) to avoid functional difficulties consequent to nonuse over a long time. Blackfield,[4] however, achieves the same result by instructing the parents to spread the lids manually for short periods each day; this would eliminate one of our current indications for irradiation. A rare case is seen with respiratory difficulty due to laryngeal involvement by hemangioma; in such cases we have considered irradiation indicated to relieve the obstruction.[8, 11]

Complications

A rare complication in hemangioma is bleeding into the lesion with associated thrombocytopenia. Good et al.[9] reported 3 cases and cited 7 in the literature dating back to 1940. We have seen two such cases: one was not treated, and the patient died; the second was irradiated sufficiently to decrease the size of the lesion, and the patient recovered from the platelet deficiency (Fig. 77). Platelet transfusions were also given. Most of the cases in the literature were treated, usually with radiation, but some with excision, with recovery, but one patient recovered without treatment, the thrombocytopenia disappearing with the spontaneous involution of the lesion. A second patient received only 300 roentgens without effect on the tumor or the platelet deficiency, but recovered later after spontaneous regression of the tumor. At present we are not certain that treatment is imperative when this complication develops, but in view of the potential gravity of the situation it probably would be undertaken.

Fig. 77. A, Hemangioma at age 7 weeks. A small submental lesion was present at birth and gradually enlarged. At 4 weeks of age rapidity of growth increased, and the lesion oozed blood on trauma. At 7 weeks the lesion was hard and dark red with a warm, glistening surface, features at variance with the usual infantile hemangioma. Biopsy was advised and reported as hemangioma. Generalized petechiae developed; the platelet count was 34,000. X-ray treatment was administered (500 roentgens in 5 days to a field 6 by 7 cm.) and platelet transfusions given. B, At age 14 weeks. There was pronounced decrease in bulk, no petechiae were present, and the platelet count was rising.

Roentgen Therapy

The teaching that the involuting type of hemangioma is a remarkably radiosensitive lesion merits examination. A lymphoblastomatous nodule can be made to disappear macroscopically with a dose of 400 roentgens at one sitting given to a small area, and in many instances there will be no recurrence. In our experience this dose, though often producing mild to moderate decrease in bulk, will almost never produce im-

mediate complete regression of a hemangioma in an infant; in our cases of the past this was seen only once. For complete ablation by irradiation a larger single dose or multiple smaller doses are required. This type of hemangioma is considerably less radiosensitive than the lymphoblastomatous neoplasms.

In the past it was often our practice to administer one or two small doses of x-ray radiation during the growing phase of the lesion. Usually for small lesions a single dose of 300 roentgens (air) of superficial radiation was used. For large lesions a larger dose, 500 to 600 roentgens, was given, but spread out over a period of 5 or 6 days. The intent of this therapy was not ablation of the lesion, but limitation of its growth. After such treatment there may be (1) no reduction in size (indeed, in some growth may continue), (2) mild blanching of surface color, (3) slight to notable reduction in color and bulk which is maintained, or (4) reduction followed by enlargement of the lesion again to or almost to its original size (Fig. 69) (this will not occur if the lesion has passed beyond its growth phase). Serious doubt exists in our minds whether significant limitation of growth has been achieved within this range of dose. We would not favor a higher dose range.

Parent Counselling

After identification of a hemangioma as the involuting type, the parents are informed of the natural course of this disease and that our objective is eventual total regression without late undesirable sequelae. If the parents accept our recommendation, a program of periodic observation is outlined. Color transparencies are made and accurate descriptions and dimensions recorded. They are informed of existing differences of opinion about treatment of these lesions, fortifying them against critical comments by relatives and friends on the lack of aggressive action. Color transparencies have special value. Parents often find it difficult to appreciate the gradual and subtle retrogression; comparison on later visits with the initial color pictures showing unappreciated changes gives them assurance of satisfactory progress. Once involution has begun, periodic observation becomes important only for reassurance of the parents, if they require it, and for academic interest in accumulating data. Periodic observation is, however, imperative until obvious regression has started, to make completely certain that the initial identification of the lesion as one which will regress was correct. Only one patient with a lesion identified as the eventual involuting type did not show substantial regression by five years of age even though x-ray treatment had been given on two occasions.

Principles of Treatment

In most instances the management of these cases is simple, requiring only periodic observation and patience (Fig. 74). With large lesions (Fig. 67) the difficulties increase and may tax both the parents and the physician. Ulceration, which often becomes infected, may occur in small lesions, but is more consistently seen in the large tumors (Figs. 67, 75, 76) (20 per cent of the lesions in our series showed some degree of ulceration during the course of the disease). This complication has been treated by warm wet compresses followed by bakes, local and systemic antibiotics and occasionally with small doses of x-ray. In 3

A B

Fig. 78. A, Hemangioma at age 6 weeks. The patient was born with widespread hemangiomatous involvement of the face. By the twelfth day of life 6 areas of ulceration had developed. These persisted and resulted in necrosis and destruction of part of the upper lip and the left ear. The patient was first seen at 6 weeks of age. Treatment consisted in small doses of x-ray, soaks and bakes. The ulcerations healed by 4 months of age, but involution did not become apparent until age 8 months and consisted in irregular blanching. *B*, At age 22 months. After its onset at age 8 months regression continued rapidly, and only slight traces of color remained at age 22 months, when the patient was ready for plastic repair of the lip and the ear.

cases necrosis with gross tissue destruction developed early in the course of the disease and was present on admission within 12 days of birth in the case illustrated in Figure 78.

Conservative management is particularly important in the extensive lesions. Surgical excision may be a practical (but not an essential or necessary) method of treatment for some small, suitably located lesions, but in many of the large ones deformity and scarring would result. If radiation is used to the extent of eradication, some degree of late radiation damage is almost unavoidable. In the management of the extensive lesions one or more periods of hospitalization may be required. Hemorrhage rarely occurs from these hemangiomas. Such bleed-

ing as occurred in three or four cases in our series has been readily controlled by a compression bandage.

Spontaneous Regression vs. Treatment

The phenomenon of spontaneous regression in these lesions has slowly gained recognition. The literature of the past six years contains multiple reports confirming Lister's observations. Brain and Calnan[5] in 1952 reported 467 lesions treated with radiation methods and 147 untreated. The results in the untreated group were considered equally satisfactory with those treated; the only difference noted was that involution was somewhat slower in the untreated cases. Ronchese[16] in 1953 was able to follow up 33 of 59 lesions untreated and found complete disappearance or only slight residua in 24, no change in 4 (but the follow-up period in these was only 1 to 2 years); the parents obtained surgical or

TABLE 20. *Results in Hemangiomas*[16]

	UNTREATED	CAUTERIZATION	IRRADIATION	SURGERY
Number of lesions	60	68	62	136
Satisfactory result	77%	35%	24%	22%
Moderately satisfactory result	20%	50%	40%	41%
Unsightly result	2%	15%	35%	37%

radiation treatment at the hands of other physicians in 5. Ronchese[16] cites data of a comparison of results of treatment given by G. Van der Werf in a thesis published in Amsterdam in 1952. As seen in Table 20, the results appear most favorable in the untreated material.

Wallace[18] in 1953 reported 411 lesions followed up for 7 years without treatment. In 33 per cent it became impossible to detect the site of the original lesion. Slight atrophy of the skin was present in 57 per cent, and in 7 per cent slight infiltration persisted. No involution was observed in 3 per cent of the lesions; the author does not give the early growth pattern in these failures. Walter[19] in 1953 compared 88 treated (irradiation) with 83 untreated lesions. Results at the end of 5 years were considered satisfactory in 94 per cent of the treated lesions and in 96 per cent of the untreated lesions. One series treated with 400-roentgen doses showed the same speed of regression as the untreated; an increased rate of regression was observed with doses of 800 roentgens. A higher dose level of 1200 to 1500 roentgens was condemned because of the occurrence of cosmetically poor end-results in 15 per cent, due to radiation skin change.

Bivens[2] in 1954 reported on 200 untreated strawberry nevi. Forty-one per cent regressed completely, 19 per cent were fading, 11 per cent were currently being observed, no follow-up was available in 24 per cent, and

in 5 per cent the parents had insisted on treatment. Of 5 subcutaneous ("cavernous") lesions, one was removed surgically with a resultant partial facial paralysis; the other 4, untreated, regressed completely in 2½ to 5 years. Modlin[14] in 1955 reported 39 untreated capillary hemangiomas, of which 24 disappeared completely at 1 to 4 years of age, 14 were showing definite and continuing regression and 1 no regression, but the infant was only 5 months old at the time of the report. Blackfield et al.[3] reported in 1957 that spontaneous involution had occurred or was occurring in more than 200 involuting types of hemangiomas which had received no treatment. Jacobs[10] in 1957 reported 105 strawberry nevi observed for more than 1 year with total regression or satisfactory regression in progress in 97 per cent. Of much interest is this author's study of the incidence of angiomas in 1735 consecutively examined children in routine private pediatric practice. The incidence of strawberry nevi or detectable remnants of nevi dropped

TABLE 21. *Incidence of Strawberry Nevi in Routine Pediatric Practice*[10]

AGE	NUMBER OF CHILDREN EXAMINED	INCIDENCE OF ANGIOMAS (PER CENT)
Birth to 1 year	645	10.1
1 year-3 years	484	8.1
3-5 years	274	2.9
5-15 years	332	1.5
Total	1735	

from 10.1 per cent from birth to 1 year of age, to 8.1 per cent from 1 to 3 years, to 2.9 per cent from 3 to 5 years, to 1.5 per cent from 5 to 15 years of age—clear evidence of the involutional characteristic of this lesion (Table 21).

SUMMARY

The observations by Lister published in 1938 on the fate of untreated hemangiomas in infants defined the natural history of most of the lesions encountered in infancy and demonstrated that they regress spontaneously. The noninvoluting types of hemangioma constitute a minority in the infant. Lister's observations have been repeatedly confirmed by a number of authors during the past decade and are in accord with our own experience. The basic policy in the management of a hemangioma in an infant, identified as the involuting type on the basis of its growth pattern during the first few months of life, should be conservatism. Few if any such lesions require active treatment of any kind. Experience suggests that the best cosmetic results are to be obtained by letting nature take its course. Conservatism is of especial importance in the large advanced lesions.

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University Hospital
Ann Arbor, Mich.

LYMPHANGIOMAS

TAGUE C. CHISHOLM, M.D.

BERNARD J. SPENCER, M.D.

FELIX A. MC PARLAND, M.D.

Lymphangiomas constitute a bizarre yet not too uncommon group of tumors in infancy and early childhood. They are made up of amber lymph- or white chyle-containing spaces of various sizes ranging from a few millimeters to several centimeters in diameter. These cystic spaces are lined with flat endothelial cells set in a connective tissue stroma of varying density. Often this supporting stroma has scattered collections of round cells and/or tiny lymph nodules. The exact nature of these honeycomb collections is not established. Many observers assume that they arise from misplaced embryonal islands of connective tissue and lymph vessels; a few look upon lymphangiomas as true neoplastic growth; and several are convinced that some congenital factors are in operation, since their appearance is consistently in infancy and early childhood.

Most lymphangiomas are slowly growing tumors in a single location. Few develop rapidly, and rarely do they appear to be multicentric in origin. The largest numbers have been reported in the neck, axilla, groin, mediastinum, abdomen and in the extremities. Occasionally they have been found in the orbit, eye, tongue and on the trunk.

As lymphangiomas grow, their endothelial buds penetrate fascial planes and engulf nerve fibers, blood vessels, muscles, fat and tendons. They develop multiloculated pockets full of lymph which know no bounds. Whether the Greek term *hygroma* (*hygros*, water, and *oma*, tumor) was selected as an appropriate name to describe the "water" content or the manner of "flowing" by extension is subject to speculation.

Although these tumors may not kill by metastases, nevertheless they

may behave malignantly in a single location by invasion with local tissue distortion and destruction, by bleeding and necrosis or by infection. As such they may interfere lethally with such vital processes as swallowing, breathing, digestion and locomotion.

CYSTIC HYGROMAS OF THE NECK, AXILLA AND GROIN

Cystic hygroma is the most common variety of lymphangioma in the entire pediatric age span. Nevertheless an individual pediatrician or family doctor may encounter only one or two in a lifetime of practice. Cervical hygromas appear 40 times more frequently than in the axilla and 60 times more frequently than in the groin. In all three locations the hygroma may appear as a tiny, soft, ovoid mass which is superficial under the skin. Other hygromas are larger, multiloculated and more deeply penetrating the fascial planes among muscles, nerves, vessels and tendons. A few are enormous and can interfere with vital processes, such as passing through the birth canal. They may obstruct the trachea, or displace the tongue out of the mouth, and thus complicate deglutition.

The great threats to life with cystic hygromas are from extension, infection and hemorrhage. Deep x-ray treatment and/or radon seed implantation have long since been abandoned for lack of uniformity of success. Surgical excision is the treatment of choice. The age of election for surgical removal is the age when the diagnosis is established. Too often hygromas appear as tiny tumors, and their removal is deferred. Two days or two months later the endothelial buds have extended into and around vital structures. Sudden trauma is sometimes associated with massive hemorrhage; at other times a mild upper respiratory tract infection is associated with acute infection in the hygroma with massive swelling and serious complications. What originally could have been a simple excision now has been converted, by delay, into a radical dissection often requiring the sacrifice of vital parts.

The basic principles of excision as soon as the diagnosis is made, of never doing aspiration, of performing a tracheotomy when necessary, of not being deceived by tiny superficial appearances and of routinely x-raying the chest before operation are highlighted by the following case reports.

Case I. E.H. was born with a single soft lobule of cystic hygroma in the left supraclavicular fossa (Fig. 79). On the fourth day of life, with a chest x-ray showing no mediastinal extension, with a cutdown in place for the administration of blood and with an endotracheal tube inserted for controlled respirations, the lesion was removed. The redundant, wrinkled prunelike skin slowly flattened out over the ensuing months. The final cosmetic result at 4 years of age was practically invisible (Fig. 80).

Fig. 79.

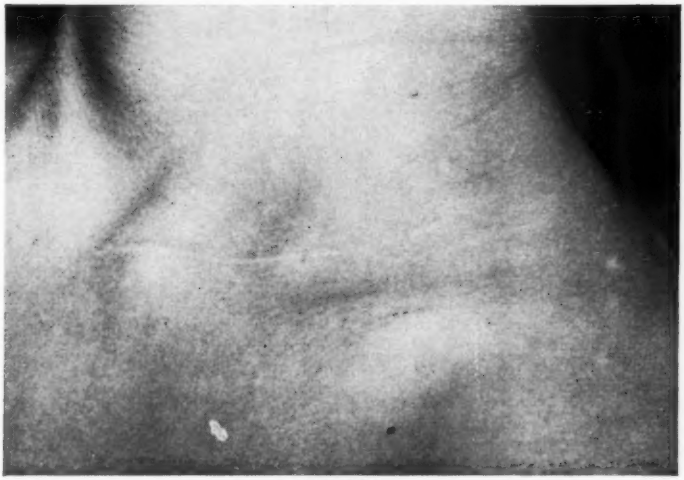


Fig. 80.

CASE II. R.S. was born after 2½ days of difficult labor. Why this enormous, multiloculated supraclavicular hygroma (Fig. 81) did not rupture remains an enigma. The infant had immediate respiratory distress. Since a chest x-ray showed no mediastinal involvement, operation was performed within 1 hour of delivery. Upon dissection the honeycombed lymphangioma extended across the trachea anteriorly, under the clavicle inferiorly, and beyond the midline posteriorly. The dissection exposed the trachea, thyroid, subclavian vessels, carotid sheath, brachial plexus, spinal accessory nerve and mandibular division of the facial nerve. Measured blood loss was replaced. A tracheotomy was needed on the first postoperative night. This tracheotomy was discon-

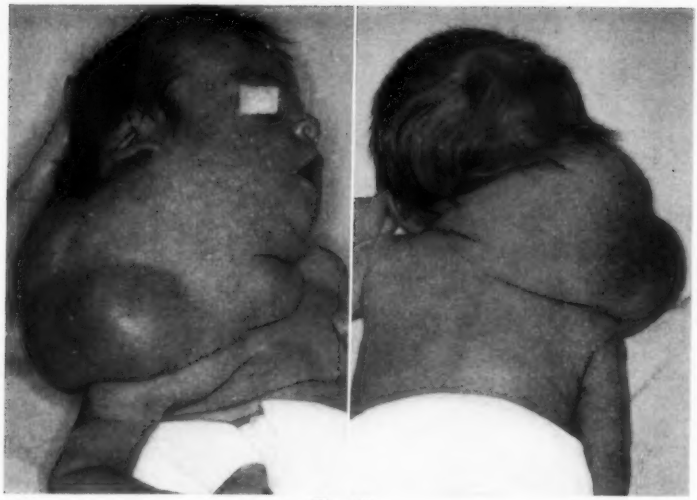


Fig. 81.

tinued after the eighth postoperative day. The infant fared well and went home at 19 days of age.

Case III. L.D. had a tiny, soft hygroma of the right supraclavicular fossa at the time of birth. Nothing was done because the infant was "so tiny." By 6 weeks of age

Fig. 82.

the lesion had enlarged a little. On a Saturday night aspiration was done in a physician's office. Several ounces of amber-colored lymph were removed and a pressure dressing applied. Late that evening the infant was found in hemorrhagic shock with a recurrent swelling. At operation several hours later the honeycombed hygroma was filled with clotted blood (Fig. 82) which represented by measurement one third of the baby's estimated blood volume. Convalescence was not unusual.

Case IV. M.H. had a moderate-sized lymphangioma in the right supraclavicular fossa at birth. At 3 months of age the lesion (Fig. 83) was not much larger externally, but at operation the cysts were found under the scapula and invading the thoracic cage at the apex of the right lung. One can only speculate about the onset of deep invasion. Many hygromas are like icebergs, with only one tenth of the mass seen

Fig. 83.

above the surface. Postoperatively, this baby had a winged scapula from permanent spinal accessory nerve damage.

Case V. S.S. had a tiny left cervical hygroma noted at birth. This disappeared by 3 months of age. At 22 months of age the hygroma recurred along with a severe tonsillitis and laryngitis. The multiloculated lesion (Fig. 84) became infected, and several weeks of chemotherapy were needed to control the deep cellulitis of the neck before surgical excision could be performed. The scar was not attractive, and satellite recurrences have required 2 subsequent surgical excisions. One wonders whether perinatal surgery might have foreshortened and simplified this course.

Case VI. K.M. had a simple cervical hygroma removed at 2 months of age. No x-ray of the chest was taken at the time of original surgery. Eighteen months later she began having bouts of dyspnea and cyanosis. She nearly died in her physician's office and was saved only by an emergency tracheotomy and intubation with a stiff urethral catheter. Upon hospitalization she was noted to have a mediastinal tumor. Through a transverse sternal incision several large hygromatous cysts were removed from the posterior mediastinum. Two of these were acutely inflamed and were obstructing her trachea. Elective excision at 2 months of age could well have avoided this near catastrophe.

Fig. 84.

CASE VII. L.K. was born with an enormous left axillary hygroma (Fig. 85). Operation was deferred because of her size. The lesion became superficially excoriated and infected. The left breast became involved. At operation the entire contents of the

Fig. 85.

axilla was exposed. The cysts extended under the clavicle, into the pectoralis muscles and into the left breast. Excision was difficult. The flaps were decompressed with suction catheters for several days. The lymphedema of the arm is only slowly subsiding with the passage of many months.

Several times the preoperative diagnosis of cystic hygroma has been incorrect. In the authors' series of more than 60 lymphangiomas some tumors thought to be cervical hygromas have eventually been diagnosed as lipoma, teratoma, neuroblastoma, Hodgkin's disease, branchiogenic cysts, and most recently a malignant carotid body tumor. No matter what the preoperative diagnosis is, a preoperative chest x-ray is essential; approximately 10 per cent of cervical hygromas have mediastinal involvement.

LYMPHATIC CYSTS OF MESENTERY AND OMENTUM

Lymphangiomas in the abdominal cavity are rare. Their location is at the whim of nature; we have encountered lymphatic cysts from high along the lesser curvature of the stomach to low in the mesentery of the rectosigmoid. None are malignant histologically, and none metastasize, but many can behave malignantly by way of invading and obstructing the bowels with acute infection, necrosis or hemorrhage. The clinical picture varies tremendously according to the immediate factors affecting the lymphangioma. A few illustrations will indicate some of the problems encountered.

Case VIII. M.V. was a 5-year-old girl who came into the hospital with a 48-hour history of anorexia, nausea and vomiting. Abdominal pain started around the umbilicus and shifted to the left lower quadrant. Her temperature was 101.4° F. by rectum. She was toxic. Abdominal tenderness and guarding were confined to the left lower quadrant. The white blood cell count was 27,000, with 89 per cent polymorphonuclears. At operation she had a wedge of mesentery near her mid-jejunum which was studded with tiny lymphatic cysts ranging from a few millimeters to 1 cm. in diameter. A cluster of these was acutely inflamed. Because the first and second vascular arcades were not involved we were able to do only a mesenteric resection without disturbing the jejunum. There has been a satisfactory 8-year follow-up without recurrence.

Case IX. F.N. was a 19-month-old boy sent in by a rural physician with the tentative diagnosis of acute appendicitis with a right lower quadrant periappendiceal mass. At operation the sigmoid mesentery (Fig. 86) was studded with lymphangiomatous cysts ranging from 1 to 9 cm. in diameter. Several of these close to the sigmoid were full of pus, whereas neighboring lymphatic cysts contained clear, amber, uninflamed lymph. A primary resection of the midsigmoid and cysts was curative.

Case X. D.R. was a 7-year-old boy who had been hospitalized 5 times in 2 years for careful evaluation of chronic recurrent abdominal pain and intestinal malabsorption. Never was a specific disorder diagnosed. At 7 years of age he was involved in a tobogganing accident and came to the hospital in profound hemorrhagic shock. At operation several lymph-filled spaces (Fig. 87) honeycombed the ileal arcades, but adjacent lymphangiomatous spaces contained 1100 ml. of freshly clotted blood. The neighboring ileum, together with the mesenteric cysts, was resected with a primary ileal anastomosis. During the past 4 years this boy has had no further symptoms of recurrent abdominal pain or malabsorption.

Fig. 86.

Fig. 87.

CASE XI. A.C. was a 2-year-old girl who came to the hospital with acute intestinal obstruction. At operation she had a dumbbell-shaped, chylous lymphatic cyst in the mesentery of her ileum which, without previous symptoms, suddenly twisted into a segmental volvulus, causing complete intestinal obstruction. Reduction of the volvulus with resection of the lymphangiomatous cyst and its adjacent ileum was successful.

CASE XII. E.B. was a 3-year-old Negro boy who suddenly doubled over with epigastric pain while in Sunday School. In short order he had nausea, vomiting, and severe intermittent pain knifing through to his back. His abdomen became as rigid

as a board and was silent. His white blood cell count was 39,000. His blood amylase was normal. At operation he had an isolated, pedunculated lymphangiomatous cyst of the omentum with acute torsion, hemorrhage and infarction. Surgical amputation was curative.

Among the foregoing five illustrative cases of lymphatic cysts of the mesentery and omentum none were diagnosed preoperatively. In these instances the child's clinical picture justified exploration, and the lymphangiomas found were causing hemorrhage, infection, intestinal obstruction, volvulus and/or torsion. In some other patients with similar clinical pictures surgical exploration revealed intestinal duplication, Meckel's diverticulum, lipoma, congenital bands or appendicitis.

LYMPHANGIOMAS OF THE FACE AND EXTREMITIES

Many textbooks describe cystic hygromas of the neck, axilla and groin as well as lymphatic cysts of the thorax and abdomen. Too few describe lymphangiomas of the face and the extremities. The latter constitute a baffling group of pediatric tumors both in pathology and in management.

Lymphangiectasia is the term commonly used to name this group of lymphangiomas of the face and of the extremities. This label implies more of a malformation and less of a neoplastic, invasive growth. Involvement of a given area of the face or of a single body somite, such as a complete extremity, suggests a regional developmental anomaly. Yet within the involved area the lymphangioma may involve all muscles, tendons, nerves, blood vessels and even bone. In combination this variety of lymphangioma constitutes a true tumefactious malformation.

Grossly, lymphangiectasias appear as diffuse, moderately firm swellings. They have no large multiloculated cysts. The lymph spaces range in size from a fraction of a millimeter to 1 cm., and there are hundreds of such tiny lymph-filled spaces set in a dense, thickly hyalinized stroma. There sometimes are scattered foci of hemangioma mixed with the lymphangioma. These tumors are leathery firm, and unless secondary infection or hemorrhage is present no pitting edema, redness, tenderness or extra warmth is observed.

Even though surgically attacked in the newborn period, such localized lymphangiomas already involve many vital structures from skin to periosteum. Such tumors show little response to x-ray therapy except possibly to destroy any attending hemangiomatous component. Early radical surgery occasionally gets ahead of the process, but too often management constitutes multiple staged excisions in an effort to hold the lesion under control while the patient and his family learn to live with the deformity. In some instances the family and/or the patient asks to be rid of the elephantitic portion by amputation.

Four case reports will illustrate the principles involved.

Case XIII. I.N. is a 6-year-old Indian boy who was born with lymphangiectasia of his upper lip (Fig. 88). At 2 years of age radon seeds were implanted in his tumor. At 3 years he had x-ray treatment. At 4 years of age he had his first wedge resection. At 6 resection was done again. He still has a long, thick, puffy upper lip. Surgical

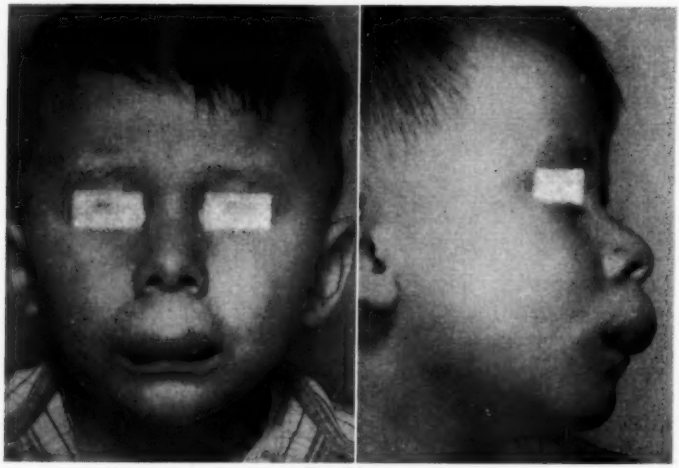


Fig. 88.

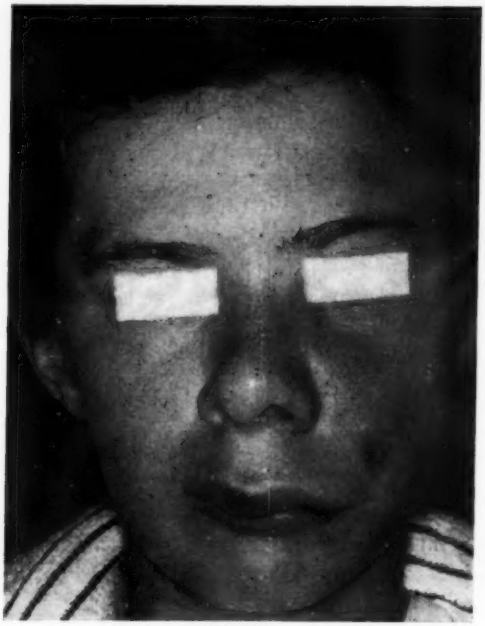


Fig. 89.

specimens always contain hundreds of tiny lymph-filled cysts set in a dense fibrous stroma. The boy has learned to live with his lesion, which no doubt will never destroy him, yet of which he will never be totally rid.

CASE XIV. M.H. originally had her lymphangioma of the left cheek treated with x-ray and radon seeds (Fig. 89). In spite of this therapy the lesion expanded, and her left maxillary sinus became obstructed and infected. This was drained by a Caldwell-Luc operation. Her lymphangioma has been subtotally removed 3 times. She has learned to live with the lesion, which will never destroy her, but numerous excisions, no doubt, lie ahead.

CASE XV. L.D. was born with a lymphangiomatous malformation of his thumb, index finger and wrist (Fig. 90). At 6 weeks of age a subtotal excision of the tumefac-

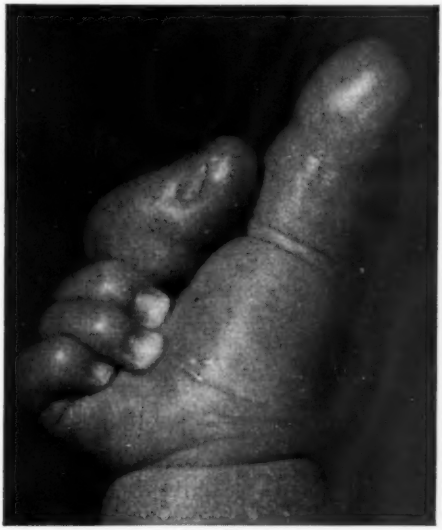


Fig. 90.

tious malformation was performed. The lesion already involved all the deep palmar spaces and their vital contents. At 9 months of age the index finger was removed to try to achieve proper alignment and relation of the thumb to the remaining fingers. Most recently the forearm is becoming progressively involved with the same process.

CASE XVI. R.R. was born with an extensive lymphangiomatous malformation of his right hand and forearm (Fig. 91, *A*). His forearm had a subtotal excision at 3 months of age. Subsequent lobules on his upper right arm were removed at 1½ years of age. By 3 he had a lump near the clavicle which has since continued to come and go. Several episodes of trauma have been followed by hematomas which intermittently have become infected and eventually sclerose. These episodes have actually contributed scar tissue which has aided in the control of the tumor size. The boy's hand and fingers have been operated upon 9 times. The lymphangiectasia of this body somite knows no boundaries (Fig. 91, *B*). The boy has learned to live with his lesion. In fact, he is nicely adjusted to his elephantitic extremity. Time alone can tell whether or not he will elect amputation.

A

B

Fig. 91.

CONCLUSION

1. Lymphangiomas constitute a bizarre group of tumefactious malformations which may occur at any site in the body. They are most common in the neck, axilla and groin, but occasionally are found in the thorax, in the abdomen, on the face or throughout an extremity.

2. Lymphangiomas or cystic hygromas of the neck, axilla and groin should be removed when the diagnosis is established, but only after an x-ray of the chest has been taken to detect possible intrathoracic extension.

3. Lymphangiomas or lymphatic or chylous cysts of the chest and abdomen often manifest themselves by hemorrhage, necrosis, infection or intestinal obstruction. Ordinarily such tumors in these cavities should be removed when they are detected.

4. Lymphangiomas or lymphangiectatic tumors of the face and extremities sometimes defy curative removal. Multiple staged surgical excisions aid in the control of the deformity. Basically, these patients learn to live with their tumefactious malformations. A few ask for peripheral amputation.

5. All lymphangiomas are benign microscopically, but may behave locally in a malignant fashion with displacement, invasion and destruction. Patients with these lesions are worthy of our best efforts at as early an age as possible.

308 Physicians and Surgeons Building
Minneapolis, Minn.

SOFT TISSUE TUMORS

DOROTHY H. ANDERSEN, M.D.

EUGENE V. PERRIN, M.D.

The term "soft tissue tumors" is applied to a group of neoplasms originating from mesoderm and situated in the connective tissue, muscle and fat of the nonparenchymatous tissue of the body.[16, 24] Tumors derived from mesoderm, but arising within viscera, such as mesenchymoma of the liver and leiomyoma of the alimentary tract, are usually excluded, as are lymphomas and tumors of bone. Tumors of ectodermal or endodermal origin, such as benign epitheliomas and enterogenous cysts, which may lie within soft tissue are also excluded. Although difficult to define, the term has practical value to the clinician and the pathologist. Authors have differed somewhat in their views as to which tumors and which portions of the body are to be included. The classification presented by Stout[24] has been followed in the main by subsequent authors.

INCIDENCE

The incidence of soft tissue tumors in childhood is impossible to determine with accuracy. On rough estimate, soft tissue tumors form between 10 and 20 per cent of the malignant neoplasms reported from various institutions.[2, 7, 9, 10, 12, 26, 28] An attempt to reach a more accurate figure by analysis of the reported series has been abandoned. The differences in sources of clinical material in the various hospitals and the different methods of classification used by the various authors have made accurate tabulation unsatisfactory.

Soft tissue tumors are exceeded in number by lymphomas, tumors of the central nervous system, sympathicoblastomas and, in some reports,

From the Department of Pathology, Columbia University College of Physicians and Surgeons, and the Babies Hospital, New York City.

by Wilms' tumor and bone tumors.[7, 9] Evaluation of the frequency of benign tumors is even more unreliable. In our laboratory they are seen about five times as often as malignant tumors.[2] By adult standards the total incidence of childhood tumors is low in relation to the total childhood population. From the point of view of the pediatric surgeon and surgical pathologist, however, the problem looms large.

ORIGIN

There are several indications that many of these tumors originate as embryonal rests according to the concept of Cohnheim.[6] The majority of tumors of the first decade of life may be so interpreted. The evidence for this concept is as follows:

1. Mixed tumors are not uncommon. These may be derived from more than one embryonal layer, or they may be composed of a variety of cell types originating in a single embryonal layer, as is the case with mesenchymoma.

2. The histologic appearance of the tumor cells often resembles that of normal embryonal cells. In some cases when the initial biopsy shows undifferentiated embryonal cells, examination several months later may show maturation and differentiation of the cell type, permitting a change of diagnosis from "undifferentiated embryonal tumor" to a definitive diagnosis such as myoblastoma or fibrosarcoma.

3. Tumors may arise in tissues which do not normally contain the type of cell found in the tumor. For example, embryonal rhabdomyosarcomas may arise in skin, colon or other tissues which normally contain no striate muscle. They may be interpreted as arising in islands of pluripotential mesenchymal cells.

Older children and adolescents may present late examples of these early tumors and also early examples of the types of tumors found in adult life.

MALIGNANT SOFT TISSUE TUMORS

Undifferentiated Tumors of Uncertain Origin

These form the largest group in most of the larger series.[2, 12, 15, 16] The cells may be indistinguishable from those of undifferentiated sympathicoblastoma or lymphoma. The latter diagnoses may be based on the location of the primary tumor in the adrenal or on subsequent development of leukemia. Some of these undifferentiated tumors appear to originate in the soft tissue. The majority first present themselves in the first five years of life, and are soon fatal. The following example is presented.

CASE I. A.A.P., a female infant 1 month of age, presented in Babies Hospital clinic with a "lump" in the right mastoid area which had been present from birth. This mass, 2 cm. in diameter at first, had increased rapidly in size and upon examination was a soft lobulated tumor measuring 7 by 5 by 3 cm. The child was otherwise well, and no bony defect was identified on a roentgenogram of the skull.

The tumor was apparently encapsulated and was shelled out from a vascular bed. The specimen weighed 90 gm., and its cut surface was composed of large lobules of firm yellow-white tissue. The tumor had a cellular, poorly delineated lobular pattern, and the cellular components varied greatly in appearance. Most were of moderate size, had little cytoplasm, round or oval nuclei and distinct nucleoli (Fig. 92). Mitoses were numerous. Spindle cells and large bizarre cells were seen marginally. In 1 focus the tumor appeared to have replaced a lymph node. A deep fibrous strand submitted separately did not contain tumor. A diagnosis of sarcoma, undifferentiated type, was made by several pathologists.

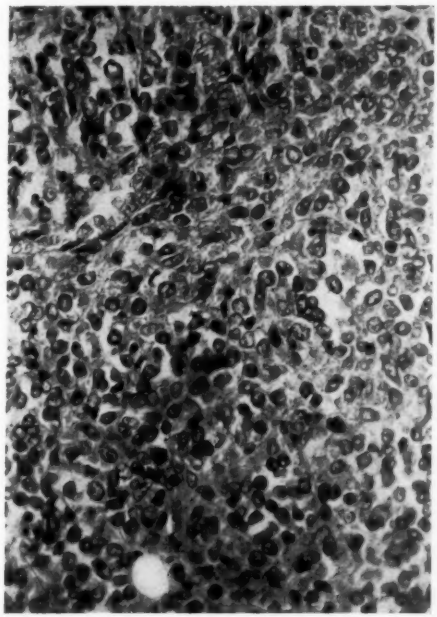


Fig. 92. Undifferentiated sarcoma, probably congenital, first excised from mastoid area in a 1-month-old girl. H&E. × 400.

Two months after excision of the primary mass, recurrence was noted at the lower pole of the scar. A group of friable nodes was removed and proved to be wholly composed of tumor elements. Radiotherapy was initiated with questionable results.

At the age of 5½ months the infant was readmitted with abdominal distention and received repeated abdominal paracenteses, which released large quantities of bloody fluid. The fluid was thought to contain cells suggestive of the primary tumor. The patient expired shortly before reaching the age of 6 months.

At necropsy, metastases were found in the right side of the neck, the lungs, liver, cervical nodes, visceral nodes, peritoneal and pleural surfaces and the fourth lumbar centrum. The largest mass was found attached to the left mesosalpinx, replacing the ovary.

Rhabdomyosarcoma

The classic type of rhabdomyosarcoma, containing whorls or bands of easily recognized, long striate muscle fibers, is relatively uncommon in childhood. It may occasionally occur in older children or adolescents. In behavior it resembles similar tumors of adult life, with a large infiltrating primary tumor arising in skeletal muscle. Metastases are few and chiefly in the lung. The thigh and the upper arm are the more common primary sites.[16] If wide excision is feasible, prolonged survival or cure may occur.

The *embryonal rhabdomyosarcoma,* or alveolar rhabdomyosarcoma (type IV in Abrikossoff's classification[1]), is far more common.[1, 4, 11, 19, 20, 27] This tumor has an alveolar or organoid structure, with rounded pleomorphic cells contained in the lacunae between trabeculae. In the center of the alveoli are numbers of granular myoblasts, while the lining cells are smaller, usually without the fuchsinophilic granules of the myoblasts. Some portions of the tumor may be composed of undifferentiated cells. Elongate spindle, "ribbon" or "tadpole" cells may be present, often more abundant in the infiltrating margins of the tumor. Careful search may reveal a few cross striations in an occasional elongate cell. In several instances the initial biopsy has appeared undifferentiated, while a later section has demonstrated alveolar rhabdomyosarcoma. The ratio of embryonal rhabdomyosarcomas to undiagnosed undifferentiated tumors in the various reported series is in part a reflection of whether the diagnosis of rhabdomyosarcoma was accepted in the absence of clearly demonstrable cross striations.

This tumor differs in behavior from that composed of predominantly large fibers. It may originate from any part of the body except the central nervous system. Our series includes embryonal rhabdomyosarcomas arising in the erector spinae,[3] retroperitoneal muscles, foot, orbit,[4] skin, lower esophagus, diaphragm[2] and liver. The variety of sites of origin and of metastases contributes to making diagnosis difficult. The tumor metastasizes early, chiefly to regional lymph nodes and bone,[3] and it invades all local tissues, including bone. After radiotherapy the tumor shrinks rapidly, but soon recurs. Our series contains no known five-year survival; most patients survived less than a year.

Case II. A 10-year-old white girl was admitted to Babies Hospital with a 3-week history of cough, loss of appetite and abdominal pain, followed by vomiting and progressive jaundice. She had become irritable and had bouts of severe abdominal discomfort.

At admission examination she was found to have icterus, weight loss and pain on right costal margin pressure by the examiner.

Hemoglobin levels were low and fell progressively. Serum bilirubin levels ranged between 13 and 15 mg. per 100 ml., direct and indirect fractions being approximately equal. The urine was positive and the stool negative for bile. Prothrombin times, serum phosphatase, amylase and choline esterase were distinctly elevated. Cephalin

flocculation and thymol turbidity values were persistently negative. The sedimentation rate rose progressively.

Persistent narrowing of the second portion of the duodenum, without obstruction, was recorded on several upper gastrointestinal tract films.

A retroperitoneal mass palpated at celiotomy proved on biopsy to be pancreas infiltrated with firm buff-gray tumor. Nodules of tumor were also found in the gastric wall and excised. The patient was discharged after recovery from this procedure.

Section of peripancreatic tissue and stomach wall contained tumor composed of several types of poorly differentiated cells lying in incomplete, elongated alveoli. Most cells were of hyperchromatic "blast" type, poor in cytoplasm, and others contained linear or dispersed, coarse eosinophilic granules and had large round nuclei. Vacuo-

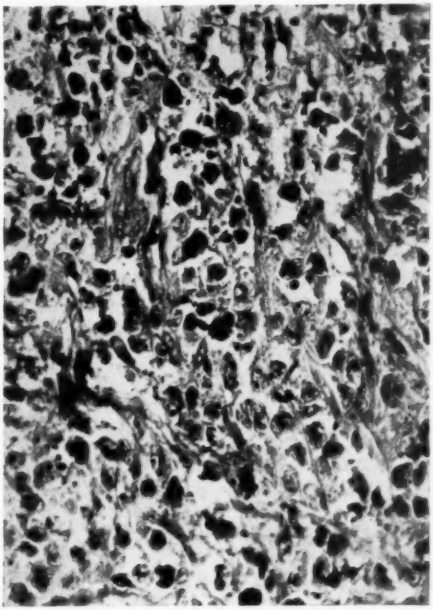


Fig. 93. Embryonal rhabdomyosarcoma. In this focus, cells lie in incomplete or loosely arranged acini. Rare cytoplasmic cross striations are present. Masson's Trichrome stain. × 400.

lated and multinucleate elements were seen, and mitoses were rare (Fig. 93). A few cross striations were found. The diagnosis of embryonal rhabdomyosarcoma was made.

A liver biopsy showed early portal fibrosis, bile duct proliferation and bile stasis, suggestive of a long-standing obstruction of the extrahepatic bile ducts.

The patient was readmitted in great distress shortly after discharge. Pain was relieved by decompression of the bladder, but physical deterioration was marked. She received intensive radiotherapy, but expired 4 months after onset of symptoms.

At necropsy the primary tumor was considered to have arisen in the retroperitoneal tissue behind the pancreas. Metastases were found in the endocardium, pancreas, adrenal, kidney, ovary, stomach, duodenum, striated muscle, thyroid and peritoneum. Frank biliary cirrhosis was present. The areas which had received irradiation showed extensive fibrosis, but with persistence of nests of tumor cells. The gallbladder was

gangrenous and the common duct obstructed. There was also a thrombophlebitis of the portal vein.

Sarcoma botryoides, a tumor forming grapelike polyps in the vagina or bladder, is closely related.[13, 14] Although the polypoid masses have a myxomatous appearance, their pedicles and the solid infiltrating tumor beneath resemble embryonal myosarcoma. Similar polypoid masses filled the pericardium in our case of embryonal rhabdomyosarcoma of the diaphragm, and such tumors have been described in the common duct.[8] It has been suggested that the formation of polyps on emerging to a mucosal or serosal surface is a characteristic of embryonal myosarcomas.

Malignant granular cell myoblastomas composed entirely of granular myoblasts are rare in children. The Babies Hospital series contains only one case; the tumor arose in the myocardium, but because of its location, is not included in the present analysis.

Leiomyosarcoma occurs infrequently. Two cases in infants, one arising in the prostate and one in the right pleura, have been reported from our files,[2] and no further cases have appeared. These are massive invasive tumors which are resistant to irradiation, but have little tendency to metastasize.

Fibrosarcoma

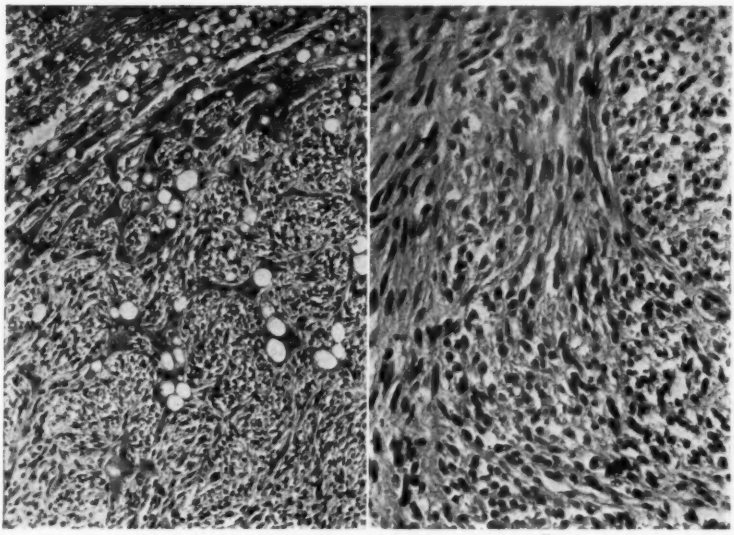
Two types of frankly malignant fibrosarcoma are represented in most of the larger series. The more common is a tumor, starting as a small nodule and growing to great bulk, which may occur at any site.[22, 24] Although it grows and infiltrates locally, it rarely metastasizes, perhaps because the large fibers of which it is composed are not readily transported by vascular channels. If the location of the tumor permits wide excision or amputation, a cure can often be achieved.

The second type of fibrosarcoma occasionally encountered in childhood is a malignant *neurilemmoma* arising in the nerve sheath.[23] It may occur as a complication of neurofibromatosis or von Recklinghausen's disease. Any nerve may be affected.

A few cases have been reported of a variety of tumors which may be considered rare in this age period; among them are malignant *synoviomas* and *fibromyxosarcomas*. The locally invasive juvenile fibromatoses of low or no malignancy are discussed with the benign tumors. Dermatofibromas occurring in childhood are as a rule clinically benign. An example of a massive fibrosarcoma is presented.

CASE III. After a careful investigation at her local hospital a 7½-year-old white girl was referred to Babies Hospital for therapy and evaluation. She had had a 4- to 5-month history of visual blurring, and a 6-week history of pain in the right axilla, followed by shortness of breath. A shadow was seen in the right thorax on x-ray examination, and a supraclavicular node biopsy was interpreted as containing spindle cell sarcoma.

When first seen here, the patient showed general glandular enlargement and



A B

Fig. 94. *A*, Fibrosarcoma, metastatic to liver, showing residual liver cord cells and the uniform pattern of tumor elements. H&E. × 120. *B*, Cells are moderately plump and uniform. Mitoses are not infrequent. The pattern is that of whorling, occasionally interlacing fascicles of closely packed cells. H&E. × 400.

evidence of recent weight loss. Breath sounds were diminished, and the percussion note was flat over the entire right side of the chest. The right hemithorax was opaque on roentgenogram, and the mediastinum was shifted to the left.

An exploratory thoracotomy was performed, and a massive growth, 15 cm. in diameter, was found to occupy most of the right side of the chest. This was encapsulated and was attached by a pedicle to the posterior upper mediastinum; tumor nodules were present on the diaphragm. An 1120-gm. tumor was removed, measuring 16.5 by 14 by 11 cm. It appeared to have been incompletely resected. The cut surface was firm, pale yellow and crossed by whorling, intertwined fibers.

The cellular pattern was that of whorled bundles of elongated cells with hyperchromatic elongated nuclei (Fig. 94). Despite the pattern, suggesting a smooth muscle sarcoma, special stains were interpreted as showing some fibrosarcomatous elements. Tissue culture did not resolve the issue.

The patient was treated with supportive measures and given radiotherapy and adrenocortical steroids without benefit. She expired 7 months after diagnostic biopsy of the supraclavicular nodes.

At necropsy, tumor was found in the right pleura, neck and right lung, and it had metastasized to the left lung, liver and skull. The tumor cells had matured somewhat, and the diagnosis of fibrosarcoma was considered well established.

Mixed Mesodermal Tumors or Mesenchymomas

These tumors are defined as composed of two or more types of cells of mesodermal origin in addition to a fibrous stroma. They are regarded as rising from embryonal rests and are therefore etiologically akin to malformations and also to extragonadal teratomas.

If the various forms be included, this is a moderately common tumor. We have seen three types of tumor which might be considered of mixed mesodermal origin. The true mesenchymoma,[16, 22] containing a mélange of immature fibroblasts, vessels, granular myoblasts, red cell islands and embryonal fat cells, is rare in soft tissues, though several of these tumors have been encountered in the liver; the latter do not concern us here. One patient with congenital mesenchymomatous tumor of the leg has been seen. These tumors may be benign or malignant.

The second form is a slow-growing localized mass usually in skeletal muscle or subcutaneous fat. It is composed of several relatively mature cell types, which as a rule include granular myoblasts and cells forming angiomatous areas. Although the variety of cell types suggests an embryonal tumor and hence potential malignancy, the individual cells appear quiescent. In our cases there has been no instance of recurrence of a tumor of this type following wide excision.

The third type is a congenital neoplastic transformation of an entire arm or leg.[17] We have seen six of these bizarre tumors. Although hemangiomatous and lymphangiomatous elements predominate, and in part replace muscle and other tissue, histologic sections from many areas may show occasional islands of granular myoblasts, embryonal lipoma cells or hematopoietic cells. Although it is possible that the tumor may contain foci of potential malignancy, these tumors have in fact been clinically benign in our experience and have followed the course of regression characteristic of hemangiomas. A case is presented.

CASE IV. A white male child was first admitted to Babies Hospital at the age of 2½ years with a history of multiple hemangiomas and swelling of the right leg and buttock (Fig. 95). His twin sister was not so stigmatized. He was hospitalized at that time for treatment of infection of the involved leg and biopsy of involved areas. The swelling involved the pelvis, groin and genitals, and a questionable mass was palpated in the abdomen. The right leg was tense, firm, cylindrical and covered with atrophic skin and discolored irregular areas. The right tibia and femur were slightly longer than the left on x-ray examination, and more ossification centers were present on the left than on the involved side. Biopsy was consistent with diffuse hemangioma on this and on a subsequent occasion.

The patient received external irradiation and radium implantation into affected areas over a 3-year period without effectively altering the appearance of the limb. At ages 7 and 8 he underwent multiple corrective orthopedic procedures on flexion deformities of the right leg, since he had never been able to walk.

Despite repair and careful ambulation, the patient had repeated infections of the involved side, and the bones of the right leg exhibited osteoporosis on x-ray examination. Amputation at midthigh level was performed at 8 years of age. Numerous large venous plexuses were found in subcutaneous tissues and muscles.

On microscopic examination tissues from various portions of the leg were remarkable for the degree of angiomatous transformation in all components. The vascular channels were large, irregular and lined by mature endothelial cells. Some venous and cavernous elements were present. Numerous focal clusters of rhabdomyoblasts were identified as well as irregular fibrous overgrowth (Fig. 96).

Fig. 95. Age 2½ years. Neoplastic transformation of right leg. The leg is tensely swollen and focally discolored, and ambulation is greatly impaired.

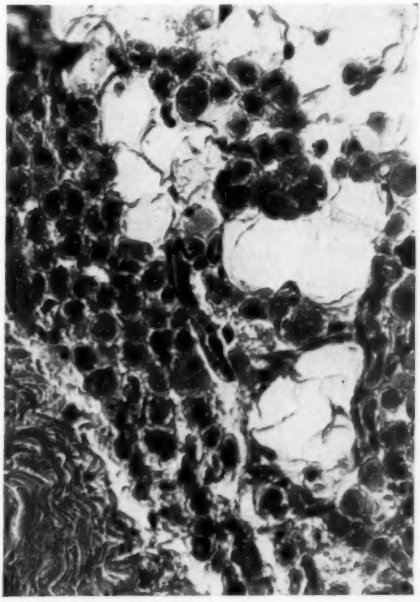


Fig. 96. Neoplastic transformation of an extremity. A nest of granular myoblasts is shown, adjacent to a thick band of dense fibrous connective tissue. H&E. × 400.

The patient was subsequently treated with radiation to suprapubic, groin and urethral meatal hemangiomas. Subcutaneous hemangiomas were excised from areas which had been irritated. Further orthopedic corrective procedures intended to facilitate prosthetic success were performed. Subsequent amputation stump biopsies at 14 years of age were diagnosed as hemangioma. At present the patient, aged 19 years, is able to work and attend school. Urethral, meatal and subcutaneous hemangiomas persist. Successful prosthesis is not at present feasible, and revision of the stump is again being considered.

Uncommon Malignant Tumors

Tumors which are rare but have been reported in children include liposarcomas, fibromyxomas, angiosarcomas, hemangiopericytomas, lymphangiosarcomas, synoviomas, melanotic progonomas, chondrosarcomas and extraosseous osteosarcomas.

BENIGN TUMORS AND TUMOR-LIKE LESIONS

Benign Tumors of Fibrous Tissue

These are relatively uncommon and are grouped by Stout under the term "juvenile fibromatosis."[25] Among the types which may be encountered are the small fibroma of skin or subcutaneous fat, the giant cell tumor of tendon sheath, dermatofibroma and ganglia. Large locally growing desmoid tumors of the skin have been reported, but are rare in childhood. Fibromatosis of the palmar and plantar fascias occurs rarely. Keloids and hypertrophic scars are similar to those in adults, but are less common.

Angiomas and Hygromas

Angiomas and hygromas of the subcutaneous fat and of muscle are among the more common tumors. A deep hemangioma may be clinically indistinguishable from a mixed mesodermal tumor with angiomatous elements prior to histologic study of the tumor. The latter tends to be more solid on palpation, while angiomas can usually be compressed.

Benign Lipomas

These are not unusual.[15] They tend to be soft, circumscribed subcutaneous masses which on section show unusually large fat cells. Generalized lipomatosis is rare, but may occur in childhood or even as a congenital lesion. Xanthomas of the skin occur in diseases associated with lipemia, and occasionally as isolated small cutaneous or subcutaneous tumors.

Idiopathic Unilateral Mammary Hypertrophy in Infants and Young Children

Included in the Babies Hospital series of tumors is a group of six cases of unilateral painless swelling of the breast. These were seen in both sexes in equal number, in ages ranging from 11 months to 5 2/12 years. In no case was there evidence of endocrinopathy, hypothalamic disease or related medication. The masses grew slowly, reaching a maximum of 7 by 4 cm. in an older child, and all appeared to be composed of pale lobulated or homogeneous, rubbery glistening tissue. None were encapsulated. Microscopically, the masses were strikingly uniform. The mammary ductules were dilated, and ductular epithelium was multilayered, orderly and focally papillary. About ductules could be seen a pale, edematous, cellular connective tissue arranged in concentric laminae. Interstitial tissue was dense, and apparently increased in amount.

These masses remained stationary after a short period of growth. Others seen clinically have regressed. In view of the rarity of malignant tumors of the breast in the pediatric age group, conservative treatment is warranted.[18] Cautious marginal biopsy may be performed if the mass continues to grow. As the cause of these swellings is not known and is apparently not hormonal, endocrine therapy is unwise and, when used, has been without effect.

Other Tumors

Other types of benign tumors are varied. Each is so rare as to justify omission from this discussion.

Among the non-neoplastic masses which may suggest the diagnosis of tumor, the most common is a foreign body abscess. In the absence of a history of trauma, a splinter, or a fall into fragments of glass, these may be difficult to diagnose. They may be recognized histologically as granulomas. An erroneous diagnosis of tumor may occasionally be made on a biopsy of erythema nodosum or of focal fat necrosis. A benign calcifying epithelioma of the skin or subcutaneous tissue may be mistaken for an osteoma.

TREATMENT OF SOFT TISSUE TUMORS

All nodules in the soft tissue should be considered with respect, and most should be widely excised at an early date. It is often impossible to distinguish the benign from the malignant tumors before histologic examination, and sometimes even after it. Tumors in children should be treated as objectively as those in adults. It is no kindness to make a narrow local excision for cosmetic reasons if there is any risk of leaving tumor tissue behind. Wide excision, or even amputation, is

preferable for both the child and the observers. An exception may be made for hemangiomas and lymphangiomas, both of which are rarely malignant in childhood and are common tumors. All circumscribed nontender masses in skin or muscle should be regarded with suspicion. Although most are benign, a few will prove to be malignant and, as a rule, curable only when small and still localized.

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3795 Broadway
New York 32, N.Y.

TUMORS OF THE BONE

JOHN A. KIRKPATRICK, M.D.

Primary malignant tumors of bone comprise one of the most important single group of tumors in children. Their incidence is not great, but they are, unfortunately, characterized by nonspecific symptoms and signs, by radiologic and pathologic manifestations which may be difficult to interpret, by the need for radical therapy and by a grave prognosis. The clinician, the radiologist and the pathologist all contribute to the final diagnosis of a bone tumor, but the contribution of each loses value when utilized alone, an accurate diagnosis being dependent upon the evaluation of all pertinent data. Because one deals with a patient who harbors a bone tumor, as well as with his family and not with the tumor alone, the clinician who is able to treat the whole patient and counsel his family must plot the course of diagnosis and therapy. To do this adequately requires a knowledge of bone as a tissue and of the natural history of bone tumors, in addition to sufficient knowledge of radiology and pathology to evaluate the contribution of these disciplines.

DIAGNOSIS

The *signs* and *symptoms* of malignant tumors of bone are relatively nonspecific. In most instances a history of pain will be obtained and examination will reveal a mass. If a mass is large, the overlying skin may be taut and erythematous and contain dilated veins. Initially, the pain may be remittent, but later, as the periosteum is involved, it becomes deep and boring; although constant, it is often worse at night. Pain may be referred to a neighboring joint and suggest arthritis; when associated with deformity of the part, the pain will be a manifestation of a pathologic fracture. Systemic signs and symptoms are

From the Department of Radiology, Temple University Medical Center, and St. Christopher's Hospital for Children, Philadelphia.

apt to be absent except in patients with Ewing's tumor; they probably reflect the destruction of large amounts of normal tissue and/or degeneration within the tumor itself.

The levels of calcium, phosphorus and alkaline phosphatase in the serum of affected children are usually not elevated; the alkaline phosphatase, however, may be elevated in some patients with osteosarcoma. In these instances the elevation is dependent upon the amount of osteoblastic activity present.

ROENTGEN EXAMINATION

Radiologic examination occupies a unique position in the diagnosis of tumors of bone. Bone, by virtue of its physical properties, casts a definitive shadow in sharp contrast with the soft tissues within it and attached to it. Therefore lesions characterized by macroscopic destruction of bone or by the formation of new bone are readily evident radiographically.

The nature of bone, its location within the structure of the body and the surgical procedures utilized in biopsy or extirpation of a lesion in bone are such that the roentgen examination substitutes for the gross pathology. The location of the process in the bone may be seen as well as the response of the bone and of the surrounding tissue to this process. Radiologic techniques are useful in the selection of an area for biopsy and in confirmation of the adequacy of the site of biopsy. The presence of other skeletal or visceral lesions may be detected by further radiologic examination and may contribute to the final diagnosis.

An awareness of the physical basis of roentgen examination is essential to an understanding of the value and limitations of this technique. Differential absorption of x-rays as they pass through matter to strike the emulsion of the film results in a radiograph. The atomic number of the irradiated material is an important factor in the absorption of x-rays; materials with higher atomic numbers absorb more radiation than do those with low atomic numbers and thus are more radiopaque. Calcium and phosphorus have significantly higher atomic numbers than do the elements comprising the soft tissues of the body, e.g., hydrogen, nitrogen, oxygen and carbon. Tissues composed of the latter elements absorb similar amounts of radiation regardless of their chemical composition; fat, however, because of a lesser density, often appears more radiolucent than other soft tissues. Focal or diffuse abnormalities of bone are recognized when the mineral content of the part is altered.

The appraisal of an x-ray film is on a physical basis, and, though the radiologic manifestations of bone tumors are associated with certain signs, these signs are nonspecific and reflect the response of bone

as a tissue to the presence of the tumor. For example, Codman's triangle, which is often mentioned as a sign of Ewing's tumor or osteosarcoma, represents new bone deposited in the area where the elevated periosteum rejoins the cortex. Elevation of the periosteum and deposition of a zone of newly formed bone may be the result of an accumulation of pus, blood or of tumor tissue beneath the periosteum, and the x-ray absorption of any one of these is the same as that of the other two. With this knowledge, then, one not only recognizes the sign, which indeed is often present, but also is cognizant of the mechanism responsible for it. Codman's triangle can thus be evaluated as a part of the total roentgen picture. Tumor tissue may fill the marrow cavity and not be evident if the destruction of bone has not reached macroscopic proportions; as a result, most malignant tumors involve more of the bone than is apparent by the usual x-ray examination.

Alterations in the physiology of bone may be appreciated by roentgen examination. An increase in blood supply results in deossification. Dead bone, on the contrary, cannot respond to variations in blood supply and thus appears opaque. Sclerosis of bone, evident in some tumors and in osteomyelitis, is the result of a decreased blood supply. It should be recalled, moreover, that the periosteum is not visible, but that the bone it produces may be seen. In the child the attachment of the periosteum is loose and vascular, so that elevation of the periosteum by underlying hemorrhages frequently accompanies trauma followed by periosteal formation of bone.

In the growing skeleton there are a number of normal variations which may give rise to difficulties in roentgen interpretation. Irregularities in the contour of bone give rise to shadows simulating periosteal new bone formation. A prominent nutrient foramen may be mistaken for a fracture or a focal area of bone destruction. Irregular ossification of secondary centers of ossification, or accessory ossicles, must be recognized for what they are. Since these variants are often symmetrical, simultaneous examination of the opposite side will usually make the significance of these clear. In this respect one must be aware that faulty angulation of the x-ray tube or faulty positioning of the part to be examined and/or of the film will result in bizarre configurations.

The aim of radiologic examination is first to localize an abnormality and to note its extent. Analysis of the lesion in the light of the physical principles of the method and of the response of bone as a tissue follows. This information is then correlated with the clinical pattern, the laboratory data and finally the pathologic findings. That the experienced radiologists may categorize a lesion in bone by virtue of having seen a similar picture in the past is not to be denied; the response of bone to many lesions tends to be constant, and recognition of specific

types of responses on the basis of past experience may be of great importance in assigning a lesion of bone to a benign or malignant class; however, in the great majority of cases the final diagnosis must rest with the pathologist and his interpretation of the histologic pattern of the offending tissue.

MORPHOLOGY

An understanding of the morphologic findings associated with bone tumors rests, as does the roentgen interpretation, on an understanding of the nature of bone as a tissue and of its histology and physiology. Bone is mesodermal in origin. From the primitive mesoderm arise mesothelium, reticulum and mesenchyma. Mesothelium, depending on its environment, differentiates into endothelium or serosal or synovial lining cells. Reticulum gives rise to the cells of the marrow. Mesenchyma differentiates into muscle, fat and a group of tissues the intercellular matrix of which is largely fibrillar. The cell common to the latter group is, in many respects, a totipotential one, i.e., the fibroblast.

The fibroblast may differentiate into the collagenoblast (fibrous connective tissue), the chondroblast (cartilage) or the osteoblast (bone). These cells are recognized histologically by their intercellular substance. The nature of the fibroblast may be illustrated in the following examples: In growing bones, invasion of the zone of provisional calcification is by granulation tissue, i.e., capillaries and fibroblasts. The latter differentiate into osteoblasts as they arrange themselves along the bars of calcified hyalin and then produce osteoid. In adult bone the fibroblasts of the inner layer of the periosteum become osteoblasts and produce new bone when disruption of the underlying bone occurs or when the periosteum is elevated from the cortex, as in trauma or tumor.

The nature of the fibroblast is particularly evident in the behavior and histology of osteosarcoma. The cells of this tumor as seen in a single section may be predominantly osetoblastic, chondroblastic, collagenoblastic or undifferentiated without an intercellular matrix; nevertheless the metastases of an osteosarcoma composed predominantly of any one of these cell types may produce bone, and the clinical course may be little influenced by the predominant cell type. These variations in the histologic appearance of osteosarcoma are of importance to the radiologist, since the roentgen appearance will vary, depending upon the amount of newly formed bone, either neoplastic or reactive, which is deposited in and about the tumor.

The criteria for judging the malignancy of cells may be difficult to define, particularly in growing bone, and it is in growing bone that

malignant tumors are most frequent. Histologically malignant cells are manifest by an increase in mitotic figures, prominence of nucleoli, excess chromatin, an increase in the nuclear-cytoplasmic ratio and irregularity of nuclear borders. Any or all of these features may be seen in young, rapidly growing cells whose physiology has been altered by inflammation or by a change in environment such as may occur with a change in the blood supply. It is apparent, therefore, that differentiation of benign and malignant tumors based upon cytology alone may be extremely difficult. The pathologist must be aware of these facts when he examines a histologic section of a lesion of bone and must delay interpretation if a definitive diagnosis is not possible. This emphasizes the need for correlative study of a suspected bone tumor. Although the experienced orthopedic pathologist does well, indeed, in the diagnosis of bone tumors, he needs the added information available by clinical, laboratory and roentgen examinations in order to attain the greatest accuracy of diagnosis.

Bone tumors, although difficult to define, are generally recognized as new growths which arise in one of the various tissues that comprise the skeleton; leukemia, however, is usually excluded. Malignant tumors are those in which there is progressive growth of cells which do not mature, but invade and have the potential of infinite growth as long as their blood supply remains intact. The two most common primary malignant tumors of bone encountered during childhood are the osteosarcoma and Ewing's tumor. These will be discussed, and then the more common lesions which must be considered in the differential diagnosis of each of them will be briefly described.

OSTEOSARCOMA

Osteosarcoma is a primary malignant neoplasm of bone arising from the undifferentiated fibrous tissue of bone. It is the most common malignant bone tumor occurring in the pediatric age group; indeed, excluding plasma cell myeloma and leukemia, it is the most common malignant tumor of bone at all ages. Approximately 50 per cent occur during the first and second decades of life, and males are affected more often than females. In the younger patients, cylindrical bones are more frequently involved than are flat bones. The youngest patient in a recent series was four and a half years of age.[4]

The femur is the most frequent site of osteosarcoma, being involved in almost 50 per cent of the cases; the distal end is the usual site of involvement of this bone. The tibia, particularly its proximal end, is frequently involved. Thus the majority of osteosarcomas involve the region about the knee. Involvement of the proximal end of the humerus is not uncommon. It is unusual for this tumor to involve the bones of

the hands and feet. The ilium is the most frequently affected flat bone. Osteosarcomas arising in cylindrical bones usually affect the metaphysis at the end of the bone having the most rapid growth. If a lesion is not metaphysial, the diagnosis of osteosarcoma, although certainly not excluded, should be suspect.

Osteosarcoma in the older age groups (over 50 years) has been reported as arising in an area of Paget's disease. An association with osteochondroma and fibrous dysplasia has been noted, but this is unusual in the young patient. An increase in the incidence of sarcomas of bone, over half of which are osteosarcomas, has been observed following deep radiation therapy to the affected bone or to contiguous soft tissues. Large amounts of radiation are common to these sarcomas, and in practically every such instance there has been evidence of damage to adjacent structures. The interval between irradiation and the appearance of the tumor has averaged 11 years.

The physical findings and *symptoms* of an osteosarcoma are usually nonspecific. The patient may sometimes present with a pathologic fracture through the involved area, but more often pain and a mass are noted. The overlying skin may be taut and erythematous with prominent vessels, depending upon the size of the underlying mass. Proximity to a joint may mimic a primary abnormality of the joint with pain and a limp. Systemic signs and symptoms usually do not occur until late in the course of the disease. An elevated level of serum alkaline phosphatase is observed in association with some osteosarcomas, but in a number of instances normal levels are observed.

Roentgenographically, this tumor presents as a metaphysial area of bone destruction with varying amounts of new bone formation in a cylindrical bone. The destructive area is most often medullary in location. It is usually irregular, poorly defined and associated with varying degrees of cortical destruction, periosteal new bone formation and a soft tissue mass. The tumor tends to be vascular, and osteoporosis may be apparent as a result of increased blood supply or of disuse of the part. The roentgen manifestations reflect the underlying morphologic changes. As a result, the amount of new bone which will be visualized is dependent upon the amount of mineralized osteoid produced by the neoplastic cells and by the response of the adjoining periosteum and osteoblasts to the presence of the tumor.

On the basis of the histologic pattern osteosarcoma has been divided into four *classes*. These represent only variations in cellular morphology; the course of the disease is the same regardless of the class of the osteosarcoma. The cellular classification of the primary tumor may not be the same as that of its metastases. Furthermore, the classes are not mutually exclusive, and, although in a given tumor one class usually predominates, more than one cellular pattern is usually present.

Class 1—the tumor is predominantly osteoblastic with the production of neoplastic bone.

Class 2—the tumor shows both osteoblastic and chondroblastic activity; when the latter dominates, the histologic pattern may suggest that of chondrosarcoma.

Class 3—the tumor is predominantly collagenoblastic.

Class 4—the tumor is made up predominantly of immature, pleomorphic cells incapable of producing an intercellular matrix.

These differences in this histologic appearance of the tumor are reflected in the radiographic appearance, and this has given rise to a radiologic nomenclature based on the gross appearance of the lesion. It is more important to understand the mechanisms responsible for the variations in the roentgen appearance than to use the variations as the basis for a classification which is purely descriptive.

As a rule, extension of the tumor through the medullary canal is greater than can be appreciated radiographically. Penetration of the cortex results in elevation of the periosteum. The "sunburst" appearance of the lesion which is often seen by x-ray reflects new bone (probably reactive and non-neoplastic bone) deposited about small vessels that stretch from the periosteum to the cortex. Where the periosteum rejoins the cortex, new bone is deposited to form Codman's triangle. Eventually the neoplasm penetrates the periosteum and invades the surrounding soft tissues. Necrosis is commonly present within the tumor.

Treatment of osteosarcoma is by surgery. The lesion is resistant to the usual amounts of radiation, but this modality must be used if the area involved is not amenable to radical surgery. Some have advocated radiation therapy in rather large amounts followed by amputation. Any form of therapy must be preceded by a definitive histologic diagnosis. This is preferably made by examination of material prepared by frozen section, but if doubt as to the diagnosis exists, permanent sections must be examined. These should be available for study within 24 hours, and, if the diagnosis of osteosarcoma is established, immediate therapy should be instituted. Amputation is performed preferably through the bone above the one containing the tumor and between two tourniquets. If amputation is performed through the bone containing the tumor, tissue from the stump should be examined for neoplasm, and, if such is present, further resection should be performed. Lymph nodes are rarely involved.

Osteosarcoma metastasizes to the lungs and only rarely to other bones. The metastatic tumor may contain bone regardless of the histologic class of the primary tumor. In the untreated or inadequately treated case, metastases occur early, and the *course* of a patient with osteosarcoma is usually about 18 months after diagnosis has been

established or 6 months after the appearance of pulmonary metastases. Resection of solitary pulmonary metastases has been utilized with an increase in survival of the patients.[6, 8]

The *prognosis* in osteosarcoma generally has been reported to be very poor, with an expected 5-year survival of only about 5 per cent. Recently, however, Dahlin[4] reported a series of 469 cases of which 97 per cent were traced. There was a 5-year survival of 19 per cent and a 10-year survival of 15 per cent. Admittedly, even these figures are not high, but they are certainly of such magnitude as to make early and definitive therapy mandatory. The clinician must think of the possibility of osteosarcoma and request appropriate consultation; the clinician, the radiologist and the pathologist must be aware of the nature of the process and the differential diagnosis so as to interpret their material correctly. The diagnosis must be established without delay, but must be unequivocal. The 24 hours necessary for preparation of a permanent section, if a frozen section is not diagnostic, present a much lesser danger to a child with an osteosarcoma than does amputation to a child with a benign process simulating osteosarcoma.

EWING'S TUMOR

Ewing's tumor is the second most common malignant tumor of bone encountered in the pediatric age group. It arises from the medullary tissue of bone and as such may be logically classified with the myelomas. It is most frequently observed during the first three decades of life, usually between the ages of 10 and 20 years. Ewing's tumor is more apt to occur than is osteosarcoma in children less than 10 years of age and has been reported in an infant 7 months of age. The incidence is said to be slightly higher in males than in females.

In patients under 20 years of age the tumor is apt to involve a cylindrical bone, most frequently the femur or tibia. In those over 20 years of age involvement of flat bones is more common, predominantly the bones of the pelvis, the scapulas and the ribs. It is of interest that this distribution in cylindrical and flat bones parallels the distribution of hematopoietic tissue in these different types of bone at comparable ages. Involvement of the small bones of the hands and feet is more common than in osteosarcoma. The location within a cylindrical bone is not as precise as is that of osteosarcoma, and approximately 50 per cent of the Ewing's tumors arising in cylindrical bones are located in the mid-diaphysis; the remainder involve the metaphysis and rarely the epiphysis.[14]

The *signs* and *symptoms* of Ewing's tumor are related not only to the location of the tumor, but also, in contrast with most malignant tumors of bone, in many instances to the presence of systemic mani-

festations. The predominant symptoms are pain and tenderness over the involved area which may be noted before a mass is palpable. This tumor invades and penetrates the cortex early to reach the extraosseous nerves and tissues, and therefore local manifestations may be prominent early. Fever and leukocytosis are frequent in patients with Ewing's tumor. The temperature approaches 101° F. and the white blood cell count 20,000. These findings probably reflect necrosis of tumor tissue, since grossly the necrotic semiliquid tumor may closely simulate pus.

Ewing's tumor is characterized *radiographically* by bone destruction. Classically, the medullary canal is first involved, then the cortex, followed by a large, soft tissue mass. The medullary destruction is seen as mottled radiolucencies, replacing trabeculae of bone and having the density of soft tissue. Cortical involvement is seen early as small areas of radiolucency and finally of irregular discontinuity. Periosteal elevation is common, so that a Codman's triangle may be seen where the elevated periosteum rejoins the cortex. The elevated periosteum produces a fine layer of new bone; this may be perforated at one or more sites, and again the periosteum is elevated and stimulated to the production of new bone. These layers of periosteal new bone have given rise to the "onion-skin appearance" that may be evident radiographically. Calcification is uncommon within the soft tissue mass of tumor and, when present, represents fragments of periosteal new bone engulfed by the tumor. In some instances radiographically evident bone destruction may be minimal, but the extraosseous mass immense and visible radiographically by virtue of displacement of more radiolucent muscle planes composed of fat. Such a tumor mass may be associated with involvement of the cortex simulating erosion secondary to a contiguous neoplasm primary in the soft tissues. Vascular obliteration may result in devitalized bone which appears opaque and sclerotic, and this may increase the similarity of the roentgenologic appearance to that of osteomyelitis. Although much less common than in osteosarcoma, a "sunburst" of bone may be evident about the tumor as a result of periosteal elevation.

There is generally more extensive medullary involvement than is evident radiographically. The semiliquid tumor and necrotic bone found at surgical exploration may closely resemble the material associated with infection, and *histologic examination* is necessary in order to differentiate these lesions. Histologically, the neoplasm is cellular, the cells being undifferentiated and the fields of dark-staining cells tending to be irregularly divided by bands of fibrous tissue. The nuclei may vary somewhat in size when examined closely, and the cytoplasm may stain clearly, with intact cell membranes, or the nuclei may appear naked. Degeneration of the tumor and considerable amounts of necrotic and reactive bone are characteristics of this tumor which add

to the difficulty of histologic diagnosis, particularly by the frozen-section technique.

Opinion is divided as to the *treatment* of the primary tumor. It does respond to radiation therapy, and many advocate using only this form of treatment of the primary neoplasm. Certainly radiation therapy is indicated when the tumor is in a site not amenable to surgery, and such therapy has definite palliative value. On the other hand, amputation through the bone above the one involved is favored by others. The survival is too small at present (about 5 per cent 5-year survival) for adequate evaluation of either method alone or in combination with chemotherapy. Metastases are usually apparent within six months of diagnosis, most frequently in the lungs, although osseous, visceral and skin involvement may be observed. The radiographic appearance of the osseous metastases is identical with the primary tumor, and the relatively frequent involvement of other bones has raised the question of a multicentric origin of the neoplasm.

DIFFERENTIAL DIAGNOSIS

During childhood a variety of osseous lesions must be considered in the differential diagnosis of a primary malignancy of bone. Some of these are generalized processes, in which bony lesions are but a part of the total process; some represent responses to injury or infection; and some are benign neoplasms. The possibility of malignancy must be considered in some instances because of the roentgen appearance, in others because of the histologic appearance of the tissue. The following lesions are some of the more common ones which must be considered and differentiated from primary neoplasms of bone.

Trauma

Unsuspected trauma to a bone may give rise to local signs and symptoms which may be responsible for roentgen examination of the area. Hemorrhage beneath the periosteum will elevate it and will stimulate production of new bone. In the case of an undisplaced fracture, roentgen examination after healing has commenced will reveal periosteal new bone and mottled radiolucency of the cortex and underlying spongiosa which may suggest a malignant tumor of bone. A biopsy will reveal evidence of fibroblastic, chondroblastic and osteoblastic activity that may closely simulate osteosarcoma. The clinician, by carefully evaluating the history and physical findings, will in this instance alert the radiologist and the pathologist to the possibility of trauma so that further study in this light will follow.

Infection

Suppurative osteomyelitis may mimic Ewing's tumor almost exactly both clinically and radiographically. Local heat, swelling, tenderness and systemic signs and symptoms such as are associated with infection may also be seen with Ewing's tumor. Infection of bone results in a roentgen picture characterized by mottled areas of radiolucency, sclerosis of bone secondary to vascular embarrassment and the production of periosteal new bone. The location of the process in the diaphysis suggests a Ewing's tumor, but almost 50 per cent of these tumors in cylindrical bones are metaphysial, as are the majority of instances of osteomyelitis. The surgeon may confuse the two conditions at the time of biopsy because of the gross similarity of necrotic tumor tissue and inflammatory exudate. Histologic examination, culture and smears for organisms will establish the definitive diagnosis.

Metastatic Neuroblastoma

It has been reported that 35 per cent[13] to 69 per cent[9] of patients with neuroblastoma have osseous metastases when first seen. A single metastasis may closely simulate a Ewing's tumor radiographically. Metastases are usually metaphysial and are characterized by medullary and cortical destruction, periosteal new bone formation (often onion-skin in appearance and at times sunburst) and a soft tissue mass. Furthermore, it is possible that in at least some instances microscopy will not differentiate the two lesions. In such instances the diagnosis of neuroblastoma may be dependent upon the finding of other similar lesions radiographically (often cranial ones) and upon the demonstration of the primary tumor. This often contains foci of calcification and may be located in the abdomen, thorax or neck. Solitary metastatic lesions are unusual, most of them being multiple and symmetrical. Clinically, the patient with neuroblastoma is usually in a younger age group and may have a history related to the primary neoplasm. Biopsy of the bone marrow may reveal the pseudorosettes of neuroblastoma, but Ewing's tumor may also involve the marrow and produce a similar histologic appearance.

Leukemia

Leukemic involvement of bone may closely simulate the histologic appearance of Ewing's tumor, but usually the clinical pattern and examination of the bone marrow will differentiate these diseases. The roentgen manifestations of leukemic involvement of bone are metaphysial bands of radiolucency as well as more localized destructive

foci, often with periosteal new bone about the area; characteristically, multiple bones are involved in the leukemic process.[15]

Chondrosarcoma

This malignant neoplasm of bone is unusual in persons less than 30 years of age; it is mentioned only because class 2 osteosarcomas may have a similar histologic appearance. The chondrosarcoma arises only from chondroblasts. In addition to a different age distribution, this neoplasm has a distinctly different clinical course and skeletal distribution. More than three quarters of these tumors arise in bones of the trunk (the pelvis and ribs predominantly), the proximal femors and humeri. Radiographically, the tumor is usually large and bulky, with the density of soft tissue, and contains streaks and smudges of calcification. The course of the disease tends to be prolonged, with local recurrence often delayed for 5 to 10 years even in the absence of radical therapy.

Primary Reticulum Cell Sarcoma of Bone

This tumor occurs in the pediatric age group, although it is more common later in life. Its skeletal distribution is similar to that of Ewing's tumor. Radiographically and histologically, it may closely simulate Ewing's tumor, although there is usually more reactive bone evident as a manifestation of its slower growth. Histologically, the cells tend to be larger and lobulated. This tumor has the best prognosis of any primary malignant tumor of bone, 40 to 50 per cent of the patients having been reported as surviving for 5 years after radiation therapy. To further the cure rate, some advocate amputation with radiation therapy to the regional lymph nodes.

Reticuloendothelioses

The osseous lesions of Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma present a fairly typical roentgen appearance when a flat bone is involved. The lesion is sharply defined, round or ovoid with no reaction in the surrounding bone. In a long bone, however, involvement of the cortex results in a destructive focus and periosteal new bone formation which mimics a malignant tumor.[7] Histologically, the lesion consists of fields of macrophages or monocytes which may simulate the cells of a Ewing's tumor. In most instances lipid-bearing cells, multinucleated giant cells, lymphocytes, plasma cells and eosinophils will be demonstrable in some areas. The clinical

pattern in Hand-Schüller-Christian disease and Letterer-Siwe disease will often differentiate these from a primary neoplasm of bone, since visceral involvement and multiple bony lesions are commonly present in these disseminated diseases. The solitary lesion characteristic of eosinophilic granuloma presents a greater problem from the clinical and roentgen aspects, but microscopy will usually establish a correct diagnosis.

Benign Neoplasms, Hamartomas and Reactive Lesions in Bones

Osteoid Osteoma. This lesion, if not examined intact under the microscope, but rather in fragments as is usual after curettage may present a histologic picture simulating that of osteosarcoma. The tissue of the central nidus consists of masses of osteoid which are irregularly mineralized, embedded in a vascular matrix of elongated spindle cells undergoing transition into osteoblasts. More peripherally there are spicules of more mature bone followed by the heavy lamellae of bone that run in a direction at right angles to the spicules. Radiographically, the lesion is seen as a small radiolucent area usually surrounded by dense bone, the nidus rarely being greater than 2 cm. in diameter. Clinically, the patient presents with pain, progressive and constant over a period of months, which is often worse at night. If the lesion is near the skin, there may be point tenderness. Surgical removal is curative.

Benign Chondroblastoma (Codman's Tumor). This benign neoplasm, which arises from young chondroblasts in the epiphysial plate, involves primarily the epiphysis and is most common during the second decade of life. To the pathologist the large number of cells of uniform size in a matrix of hyalin, myxoid material and collagen (often with areas of calcification) may suggest chondrosarcoma or osteosarcoma. The roentgen appearance of the lesion is that of a somewhat radiolucent mottled area with a thin sclerotic border located in the epiphysis of a long bone. The tumor may extend into the metaphysis.[10] Clinically, pain is a constant feature and is often referred to the nearby joint, thus suggesting arthritis. Treatment is by curettage.

Chondromyxoid Fibroma. This is an uncommon benign tumor of bone which is of importance because of its histologic appearance, which may simulate that of chondrosarcoma. Its usual location is in the metaphysis of a cylindrical bone, where it presents radiographically as a lobulated, demarcated lesion which may erode, thin and expand the overlying cortex. As a result the patient may be seen because of fracture through the lesion, although the common complaint is that of mild and often intermittent pain. Histologically, the tumor is composed of masses of cartilage cells of various ages embedded in a fibrous

and myxomatous matrix. Giant cells are not uncommon, as well as granules of pigment, lymphocytes and neutrophils. Curettage is the treatment of choice.

There are many other benign lesions in bone that should be mentioned for the sake of completeness. As a rule they do not present the same problems in differential diagnosis as do the ones listed, and they are seen with sufficient frequency or present a more definitive pattern so as to be familiar to most clinicians, radiologists and pathologists. Any one lesion, however, complicated by trauma or infection may be exceedingly difficult to differentiate from a malignant tumor, since the basic tissues of which they are composed are those present in certain of the malignant tumors of bone. These include osteochondroma, nonosteogenic fibroma, osteoma, fibrous dysplasia and neurofibromatosis.

SUMMARY

Osteosarcoma and Ewing's tumor, although infrequent, are the two most common primary malignant neoplasms of bone encountered during childhood. Early and correct diagnosis must be made if the results of therapy are to be satisfactory. This demands the combined efforts of the clinician, the pathologist and the radiologist. Each must have a high index of suspicion with respect to these lesions as well as a broad knowledge of the more common benign neoplasms, hamartomas and reactive osseous lesions which may be mistaken for malignant neoplasm. Therapy is radical, and the over-all prognosis is relatively poor; therefore misdiagnosis and overtreatment of a benign process are to be avoided as much as is delay in treatment of proved malignant neoplasms. The diagnostic and therapeutic management of a child with a malignant tumor of bone is shared by the clinician, the pathologist and the radiologist, but the ultimate responsibility is that of the clinician, who can and must treat the whole child and his or her family.

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2600 N. Lawrence St.
Philadelphia 33, Pa.

TERATOMAS

JOHN L. EMERY, M.D.

Teratomas have stimulated the imagination of medical men of all ages, and the vast literature on bizarre deformities and tumours which have been seen in man and animals merits study perhaps more as imaginative than as scientific literature. Probably most prominent in the field today is that most charming and stimulating man, Rupert Willis, whose recent book, *The Borderland of Embryology and Pathology*, is likely to become a classic of the fundamentals of paediatric pathology. Having sat at his feet at lectures, been cross-examined by him at meetings, and been a co-examiner with him on other occasions, what I say about teratomas is bound to be coloured by his views.

There are four groups of "peculiar" growths that are frequently linked together in the minds of medical people.

1. CONGENITAL ABNORMALITIES OF DEVELOPMENT

These are often bizarre structures, but, although tumour masses in the physical sense, are not pathologically tumours, and arise by an error in general anatomical growth during the process of normal development. They are under the same growth control and react simultaneously to general stimuli as the normal organs of the body. The error in the organisation of growth can occur at any point before the adult stage of an organ is reached.

2. HAMARTOMAS

Hamartomas are tumour-like deformities, but consist of the normal mature tissues of the site of their location. They differ from the local normal tissues only in that the different tissues present are in abnormal proportions, e.g., an angioma. They differ from embryomas and teratomas in that they are not tumours in the pathological sense, and, like

congenital deformities, are governed by the general mechanisms of growth—they are quantitative but not qualitative abnormalities.

3. EMBRYOMAS

Embryomas are tumours. They arise in an already formed organ of the body and contain the elements of that organ or location in an embryonic state. Although the tissues of an embryoma are frequently mixed, they are not heterotropic. The tissues in them were present in the embryonic tissue from which the organ at the site of the tumour arose. Embryomas are closely related to teratomas, and are probably the most lethal tumours in children. Of them, the most common are the nephroblastoma (Wilms' tumour), hepatoblastoma, sarcomas of the connective tissue and muscle (rhabdomyosarcomas) and the tumours arising from nervous tissue—neuroblastoma, ganglioneuroma, retinoblastoma and medulloblastoma. These tumours are dealt with by other authors in this volume.

4. TERATOMA

A teratoma is a true tumour. Its essential features are that it contains many types of tissue, including tissues not normally present at that site. The teratoma contains tissues which come from all three types of embryonic tissue in varying proportions: i.e., *ectodermal* tissue, consisting of skin, teeth or nervous tissue, and so on; *mesodermal* tissue, i.e., connective tissue, vascular tissue, heart muscle, and the like; and *endodermal* tissue—respiratory or intestinal tract.

Teratomas tend to occur in the midline of the body and are rarely associated with the limbs or the peripheral aspects of any organ. They seem to arise from small masses of undifferentiated tissue in the embryo that escape the influence of the normal organisers. Although teratomas in many instances appear in the adult as malignant tumours, it is almost certain that the majority of these tumours have existed from intrauterine life in a benign form, and have developed malignant tendencies later. This would appear to be a particular feature of testicular teratomas. The amount of organisation which can take place in a teratoma is extremely various. A teratoma can contain pieces of intestine with full mucosa, muscular and nerve plexus layers. On the other hand, teratomas have been described in which the cells of one part are of different sex chromatin than other parts. When one is confronted by a teratoma containing highly organised tissues resembling limbs, the problem of whether, in fact, the teratomas are a sort of "foetus in foetu" arises, a topic which one suspects will form a discussion point for pathologists for many years to come.

The classification of tumours mentioned above is fairly simple and clear in an academic sense, and some people, notably Willis, are convinced that there is a clear distinction between these types of abnormal growth. Potter finds difficulty in categorising some tumours in this way, and I have had at times much the same difficulty.

Teratomas have been described in an extremely large number of sites in the body. Figure 97 shows in a diagrammatic form the principal sites where teratomas are to be expected in the child. It is almost impossible to gauge the absolute incidence of these tumours. Bizarre

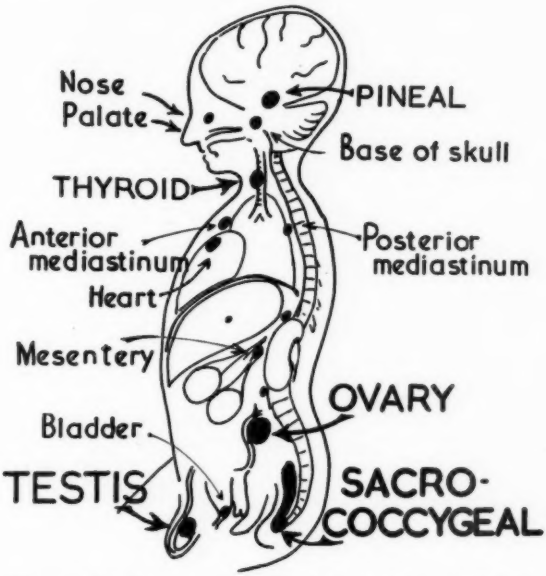

Fig. 97. Diagram showing common sites of teratomas presenting in children.

tumours in unusual sites tend to be reported, and the proportion of tumours presenting to any individual hospital depends very much upon the age of the children and the local facilities. It is not possible to describe in detail all the teratomas that can occur in any part of the body, but the principal features and presenting symptoms of teratomas of our experience are discussed. The order of presentation will be that of starting at the head and working towards the tail.

Pineal

Tumours described as "pinealomas" are probably mostly teratomas. A large number of frankly diagnosable teratomas in this locality have also

been described. These tumours, as well as exhibiting the general features of an intracranial mass, occasionally affect the hypothalamus to produce symptoms of precocious puberty. The tumours are important in that in their early stages they are apparently well encapsulated, and are probably amenable to operation. The small, dense red mass of tissue that appears to reside above the pituitary in anencephalic infants frequently contains teratomatous elements.

Nose and Palate

Mixed tumours in these regions present considerable problems in diagnosis to pathologists. A tumour which is considered by many to be a teratoma is also sometimes called a nasal glioma. This frequently presents in the very young child as a polyp-like mass in one nostril, although it can present through the skin near the eye. These tumours are of very varying malignancy. A number of these tumours have been removed with apparently complete recovery.

Base of Skull

There are a group of tumours, known sometimes as epignathi, which appear to arise in the roof of the pharynx or palate, but arise presumably in the vicinity of Rathke's pouch, and the site of tumour corresponds embryologically to the sacro-coccygeal teratomas. They can present as congenital hydrocephalus or masses projecting either in the nasopharynx or in the nose or in the palate. They can be large at birth and be associated with gross deformities of the face. Some of these tumours are benign, but the majority are described in stillborn infants.

Thyroid and Neck

These tumours can be extremely large at birth, and on occasions cause difficulty in labour. Clinically they can be confused with the more common hamartomatous cystic hygroma of the neck, and an exploring needle into one such teratoma of the thyroid was probably a factor in the death of a child in our hospital.

Case I. This little boy was born at full term, and a swelling of his neck was noticed at the time of birth. He was noticed to have stridor at times, and an attempt was made by the family doctor to aspirate the cervical mass. After this the tumour apparently became firmer, and the child had a severe cyanotic attack. He was then admitted to hospital. There a non-translucent, cystic mass was found filling the right neck, the jaw and tongue being displaced upwards. The child's condition was not good, but an immediate operation was thought necessary, and a large, almost spherical tumour was removed with relative ease, by George Avlamis, from the region of the right thyroid gland. After operation the child had further cyanotic attacks, and his condition deteriorated steadily to death at the age of 7 days.

Figure 98 shows the tumour replaced in its original site after necropsy, from which its size and position can be well judged. The child had died with multiple lung abscesses and pneumonia which had presumably followed early inhalation. The tumour was completely surrounded by a thin film of flattened thyroid tissue, and there was much haemorrhage within it. The tumour contained a great variety of tissue; there were fragments of cerebral tissue, many types of glands, both respiratory and intestinal epithelium, muscle and cartilage.

Fig. 98. Photograph of teratoma of the thyroid, presenting at birth and causing stridor.

This was a benign teratoma arising in the thyroid gland. It was completely localised, and theoretically at least, if it had been recognised and operated upon within a short time after birth, the child could have made a complete recovery.

Mediastinal

Most of the mediastinal tumours show symptoms after childhood, and are much more common in the anterior than in the posterior mediastinum. One case that we found incidentally at necropsy in the posterior mediastinum could superficially have been thought to be a duplication of the oesophagus or intestine, and but for extensive histological examination would have been diagnosed as such. Perhaps the most important group in the chest are the so-called *intracardiac teratomas*. This group is important clinically, since these tumors are rarely within the muscle of the heart. but lie in the tissues at the

base of the heart and in the pericardium. They appear to be of a benign type, and are lethal simply on account of their situation. Although these tumors are extremely rare, they would appear to be ideally suited to surgery. They should be suspected when evidence of compression of the circulation of blood occurs in a previously healthy child, and they are one of the conditions which justify routine straight and lateral radiography in cyanosis of newborn children.

Retroperitoneal Teratomas

The retroperitoneal teratomas of the upper part of the abdomen are in our experience extremely rare, and the literature suggests that they present chiefly in adult life. Some of the large cystic tumours which occur in the root of the mesentery and present as mesenteric cysts are teratomas, and we have seen one of these among a series of half a dozen intestinal duplications. These tumours appear to be benign in that they do not metastasise, but tend to be of the large cystic type and amenable to surgery.

Ovary

The ovary is the commonest site in the body for teratomas. They can present at any age, but usually do not do so until later childhood. Specimens of these so-called ovarian dermoids, which frequently contain hair and teeth, are familiar to all who have ever visited a museum of pathology. These ovarian teratomas are usually single, and most of them are benign and cystic. The tumours presenting in a small child would seem to have a greater tendency to malignant change than those occurring in later childhood and early adult life, and it would seem always justifiable to advise immediate removal of any suspected ovarian teratoma in a child.

Testis and Epididymis

These tumours are dealt with elsewhere in this volume (p. 500).

Sacro-coccygeal Teratoma

This, in our experience, is by far the commonest type of teratoma that presents as a treatable clinical problem. These tumours can present at birth as extremely large masses, larger than the child's head, and have been known to cause difficulty in labour, or they can present with symptoms of pressure on pelvic structures or viscera, and with no external signs whatsoever. Three cases are described here, which illustrate the clinical problems involved.

CASE II. A little girl was found to have a very large swelling in the region of the buttocks at birth, and apparently there was some difficulty in delivery. She was born at full term in hospital, and she passed urine and stools normally, and took feeds normally. The swelling was behind the anus, and was tense and displaced the anus anteriorly. Some parts of the tumour, however, felt firm.

Fig. 99. A large sacro-coccygeal cystic teratoma, completely treatable by surgery.

The child was transferred to hospital, and the paediatric surgeon, Mr. R. B. Zachary, carried out a tedious operation, excising much skin and part of the coccyx, and the buttocks had virtually to be reconstructed.

The child has been followed up for several years, with no signs of recurrence, and appears to be developing as a completely normal child.

CASE III. When born, this boy was thought by the family doctor to have a spina bifida and meningocoele, and was admitted to hospital with that diagnosis.

On admission a large cystic swelling was seen bulging through the pelvic floor, just in front of the sacro-coccygeal region (Fig. 100). A small amount of air and radio-opaque dye was put into this sac, and X-rays revealed a widespread cavity. He was then transferred to the paediatric surgeon, who, operating, found a mass very closely adherent to the rectum, and until frozen sections had been carried out, a diagnosis of duplication of intestines and rectum at this point was thought likely. A type of "hour-glass" constriction was found across the centre of the sacrum. Above this was a subsidiary cyst, containing thick fluid, with hairs.

The capsule of the cyst appeared to the naked eye to be largely fibrous tissue, containing a few areas of cartilage. Histologically, what appeared to be fibrous tissue contained nervous tissue, muscle, squamous epithelium, respiratory epithelium and cartilage.

The child made an uneventful recovery from the operation. Intellect and general

development continued normally. He was followed up as an out-patient for 2 years, during which time the peritoneum healed completely. There was no recurrence or other masses within the pelvis. The only slight disability which the child now has is that where the tip of the coccyx was excised, there is a slight bony prominence upon which the child occasionally sits a little too violently. This appears to represent a cystic type of teratoma arising in the region of the coccyx, which had been com-

Fig. 100. Clinical photograph of teratoma of case III.

pletely removed in the first month after birth, leaving an apparently completely normal child.

Case IV. This little girl was born at full term after a normal pregnancy. She was apparently quite normal at birth. When she was 8 weeks old, she started to pass about 5 bright green stools a day, which later became watery with much mucus. She appeared also to have abdominal pain, and projectile vomiting developed, for which she was admitted to hospital.

There was a grossly distended abdomen which was apparently due to an enlarged bladder. Eight ounces of clear urine were obtained by catheterisation, and the first clinical diagnosis was that of retention of urine due to bladder neck obstruction. Rectal examination, however, by Mr. Zachary revealed a mass in the midline in the sacral region. He was only able to demonstrate this externally when the legs were fully flexed.

Operation was carried out, and a large solid and cystic tumour was removed, apparently completely and successfully without rupture, and the child was discharged having normal control of bladder and stools, and was apparently perfectly well. Histology of the tumour at this time showed cystic spaces lined by many types of epithelium, those in the photograph (Fig. 101) showing a respiratory type of epithelium and masses of haemangiomatous-type tissue. Cartilage and brain tissue, and so forth, were found in other parts. A large number of sections were taken, and the tumour was thought to be a benign teratoma.

Six months later the child was well, putting on weight, and the wound was well healed, but rectal examination revealed the presence of 2 swellings in the pelvis. The child was readmitted and a further operation carried out, and a tumour was found filling the pelvic inlet. It was hard and attached posteriorly to the pelvis and coccyx. There was much bleeding, and the surgeon was unable to remove it all.

This tumour appeared to be completely different in texture from that previously

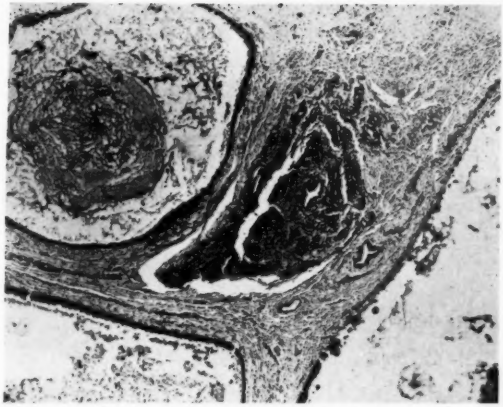

Fig. 101. Photograph of section of teratoma taken from the first operation from case IV.

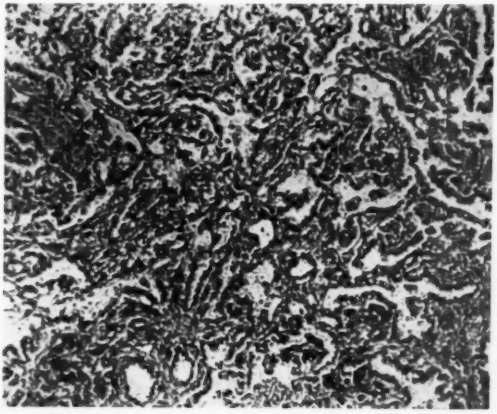

Fig. 102. Photograph of section of teratoma taken from the second operation from case IV.

examined. It was soft and friable, and the histological appearance was that of adenocarcinoma (Fig. 102). We went back to the original section and found a small area of tissue very like the later carcinomatous mass, which at the earlier time we had thought to be abnormal respiratory epithelium.

The child was treated with radiotherapy, with apparent disappearance of the tumour and all symptoms, and was discharged home. Five weeks later the symptoms recurred, with vomiting and diarrhoea. The child is now again in hospital, having a rapidly down-hill course, and is unlikely to survive to the age of three years.

This case illustrates the difficulty of diagnosis and prognosis in these cases. Clinically and on the histological examination carried out at the time of first admission, the last two cases were virtually identical. This

case stresses two points: first, the need for very extensive histological examination of a teratomatous mass, and, secondly, the great care that has to be taken in prognosis in these children.

In our experience no recurrence has been noted from these tumours after 18 months.

Western Bank
Sheffield, 10, Yorkshire
England

SOME ASPECTS OF TUMORS OF THE ENDOCRINE GLANDS

ANGELO M. DI GEORGE, M.D.

KARL E. PASCHKIS, M.D.

Tumors of the endocrine glands are uncommon in all age groups and are rare in infants and children. Wilkins[96] has collected 22 instances of tumors of the endocrine glands in 20 years. This represents 2 per cent of the patients seen during this period with endocrine problems or 1 per cent of all the patients referred to the endocrine clinic. Although most pediatricians will never encounter an instance of an endocrine tumor, these lesions must frequently be considered in the differential diagnosis of more common disorders. Thus the rare granulosa cell tumor must be considered in girls with isosexual precocious puberty, although a constitutional basis for the disorder is much more frequent. In spite of the rarity of Cushing's syndrome, the diagnosis is often considered, even if only momentarily, in most instances of obesity. The pheochromocytoma is and should be considered in the differential diagnosis of all hypertensive children. Tumors of the endocrine glands are even considered when there is little reason to do so. Medical students and house officers almost always include "pituitary tumor" in the differential diagnosis of children with precocious puberty in spite of the fact that there has never been a report of a primary pituitary tumor causing sexual precocity.

Another reason why these tumors are important is that they are often malignant and metastasize. Even benign tumors, such as the parathyroid adenoma and the pheochromocytoma, produce devastating effects as a result of excessive hormone production. Early diagnosis and treatment usually result in striking clinical improvement and complete recovery.

In addition to the important clinical aspects, hormone-secreting

tumors of the endocrine glands are of considerable interest from the aspect of tumor biology. Study of these tumors has revealed the fact that characteristics of malignant growth such as invasiveness and metastatic spread are compatible with persistence of the highly specialized enzymatic systems necessary for hormone synthesis and secretion. The fact that the secretory products can be measured quantitatively, combined with our knowledge of some agents which regulate the normal secretion of hormones (tropic hormones, feed-back mechanisms), has opened new avenues for the study of tumor autonomy and dependence. Space does not permit more than a passing reference to these interesting aspects, and they will therefore not be elaborated in the subsequent discussion of individual tumors.

TUMORS OF THE PITUITARY GLAND

Tumors of the anterior pituitary may arise from any of the three principal types of cells. *Basophilic adenomas* may be found in patients with or without Cushing's syndrome and are no longer believed to be the cause of this disorder. They do not result in enlargement of the sella, nor do they cause neurologic symptoms in children.

Chromophobe adenomas are one of the most common tumors of the pituitary in the adult, but rarely occur in children. Of a group of 77 cases of verified chromophobe adenomas the youngest patient was 17 years and had symptoms since the age of 12 years.[102] These tumors cause symptoms by pressure on adjacent structures, but not by overproduction of a hormone. They may cause pituitary insufficiency by compression of functioning pituitary tissue. Growth failure has been reported,[9, 49] as well as the usual neurologic manifestations of an expanding intrasellar lesion.

An *eosinophilic pituitary adenoma* results in gigantism if it occurs before closure of the epiphyses. This is the only pituitary tumor whose manifestations are the direct result of excessive secretion of a hormone. The age at onset and the duration of symptoms depend on the duration of oversecretion of growth hormone. Sir Jeffrey Jefferson[46] has aptly pointed out that although the name "gigantism" implies colossal strength, most of the reported cases have come under observation because the patients were failing physically and most have been weaker than men of lesser stature.

Approximately 30 cases have been reported in the world literature since 1890 under the age of 15 years.[84] It is difficult to establish the diagnosis of pituitary gigantism only on the basis of rapid growth of the skeleton and its supporting structures, since there is no rigid definition of gigantism. Signs and symptoms of an expanding intracranial lesion associated with radiographic evidence of an intrasellar lesion are

usually necessary to establish the diagnosis. Perhaps when reliable measurements of growth hormone levels are possible, diagnosis can be established with confidence before neurologic symptoms or radiographic manifestations develop.

The rapid skeletal growth is usually associated with normal osseous maturation. These patients are frequently slender and lean, and sexual maturation progresses normally at first. Arthritic changes frequently develop later in life. Many have died before 21 years of age.[46] There is usually no evidence of thyroid or adrenal disorder. Carbohydrate tolerance is diminished, as demonstrated by a diabetic glucose tolerance curve and resistance to insulin.[9, 84] The serum phosphorus level may be elevated during the phase of active growth hormone overactivity. The adenoma may eventually result in sufficient pituitary destruction to give clinical signs of hypopituitarism. Sexual immaturity and weakness then are common.

The most common conditions to be considered in the differential diagnosis are physiologic variants of growths. Children who are three or four years in advance of their chronologic age in height are not uncommon. The osseous maturation of these children is usually consistent with their height age rather than with their chronologic age, and epiphysial fusion occurs relatively early. Tall stature may be familial, and a family history is helpful in evaluating these children. Children with the various forms of precocious puberty show accelerated growth, but the advanced bone age and sexual development immediately lead to the correct diagnosis. There are no reports known to the authors of precocious puberty resulting from a pituitary tumor, although such an event is physiologically possible. Children with precocious sexual development are short as adults, owing to early epiphysial fusion. Craniopharyngiomas are the most common intrasellar tumors of children. These tumors, however, result in pituitary infantilism and growth failure. A high percentage show calcific deposits on roentgenograms.

Eosinophilic adenomas are best treated by x-ray irradiation, especially with the application of newer techniques such as high voltage rotational therapy.[42] Operative intervention should be reserved for instances that fail to respond to irradiation or in which there is rapidly progressive loss of vision.

TUMORS OF THE THYROID GLAND

INCIDENCE. There appears little doubt that cancer of the thyroid gland occurs sufficiently frequently in children and adolescents to warrant serious consideration of malignancy of the thyroid in these age groups. Recognition of this fact is fairly recent; before 1930 only 10 cases of

thryoid cancer had been reported in children. Winship in 1951[99] reviewed all cases reported in the world literature; he found 97 cases, and subsequently added 7 more. Since that time 167 additional cases reported were reviewed by the same author,[101] bringing the total up to 334 cases. This obviously only indicates a minimum of cases observed, since at present many single observations are not being reported. The question may be raised whether the increase of thyroid cancer in children and adolescents is only apparent, due to a greater awareness of the medical profession, or whether there has been an actual increase. Uhlman believes the increase to be real, although the cause for this is unknown.[87]

Perhaps more significant than the absolute number of cases reported is the statement of Duffy and Fitzgerald, who found that 6.5 per cent of 430 cases of thyroid cancer observed at Memorial Hospital in New York from 1932 to 1948 were in the age groups of 4 to 18 years.[20] In Buckwalter's[6] series of 81 cases of thyroid cancer the incidence in patients less than 20 years of age was even higher, 16 per cent.

Age Range. There is a general tendency to report incidence of thyroid cancer in young persons including an age range up to 25 years,[41] 20 years[56] or 15 years.[6] There may be some practical value and justification in this, because malignancy is not usually in the foreground of diagnostic deliberations in patients of this age range. However, from a physiologic standpoint, it appears important to subdivide the group into prepuberal children and puberal adolescents. Such a breakdown is given in some reports, e.g., in that of Buckwalter;[6] this author reports 13 cases of thyroid cancer in patients up to 20 years of age (16 per cent of all cases of thyroid cancer seen in a 5-year period); of these 13, five occurred in children less than 10 years of age. In Winship's[101] review of 334 cases of thyroid cancer in childhood a pathologic diagnosis was established before the eighth birthday in 76; the youngest was 4 months of age.

Type of Tumors. All available statistics show that 50 to 60 per cent of thyroid cancers in children and adolescents are of the papillary type;[20, 101] in a number of cases the morphologic picture is of a mixed type, showing papillary and follicular elements. However, every type of thyroid carcinoma has been observed in children, including highly malignant undifferentiated tumors.

Clinical Considerations. In 30 per cent of all cases the only presenting abnormality was a persistent cervical lymphadenopathy; in many cases a palpable thyroid nodule was present in addition to the enlarged cervical lymph nodes. In one of our cases a persistent dry cough had prompted a roentgenogram of the chest; the finding of multiple densities had suggested the diagnosis of tuberculosis, and the

girl had been admitted to the chest department. The presence of a nodular goiter and cervical lymphadenopathy, evidently ignored by the referring physician, then suggested the diagnosis of thyroid cancer. There is still considerable controversy as to the true incidence of thyroid cancer in nodular goiters in adults. There should be no such doubts in the case of children and adolescents. Winship[101] has evaluated the published reports; 27 per cent of 176 thyroid nodules in children proved to be carcinoma. The fact that a considerable number of children (15 per cent in Winfield's collected series) already have pulmonary metastases when first seen would indicate a lack of appreciation of the problem by the general practitioner and by the pediatrician.

Etiologic Factors. There is no evidence that early exposure to goitrogens is an etiologic factor in the development of thyroid carcinoma. Neither is there any evidence that thyroid carcinoma in children is more common in iodine-deficient goiter belts.[101] Evidently the duration of exposure to goitrogens and the degree of iodine deficit are not great enough to induce situations comparable to the thyroid tumors observed in animals fed thiouracil for prolonged periods of time or to the thyroid nodules developing in rats fed an iodine-free diet for a long time.

In 1950 Duffy and Fitzgerald[20] reported that 9 out of 38 cases (23 per cent) of thyroid cancer in patients below the age of 18 had been subjected to roentgen irradiation of the thymus early in life. Their conclusions at that time were cautious: "to propose a cause-and effect relationship . . . would be quite unjustified on the basis of data at hand when one considers the large number of children who have had irradiation to an enlarged thymus." Seven years later Duffy[21] found the accumulated evidence much stronger. Supporting data had come from Winship's[101] survey of the literature as well as of his own material; he estimates that about 20 per cent of the cases of carcinoma of the thyroid in children had previously received roentgen radiation to the thymus, an incidence almost identical with that of Duffy and Fitzgerald. Winship[100] had previously surveyed the increase of thyroid carcinoma in children in Western Europe and had found the incidence much smaller than in this country; he points out that thymic irradiation is not "generally practiced" in Western Europe.[101]

The concept has been broadened to include roentgen radiation of structures of the neck or upper thorax other than the thymus;[8] it has also been broadened to include other forms of cancer in children exposed to radiation, especially leukemia and osteochondroma.[73] Recently Wilson et al.[98] and Goolden[29] reported several cases of thyroid cancer in persons previously exposed to roentgen radiation of the neck.

The studies quoted above report the incidence of previous radiation in observed cases of thyroid cancer. As will be discussed subsequently, other reported series of thyroid cancer in young patients fail to give any indication of such a relationship. Furthermore, Uhlman, in a critical study of the problem referred to in greater detail subsequently, points out a basic fallacy of conclusions drawn from observations of this sort. He obtained a history of irradiation of the tonsils in 4 out of 25 cases of thyroid cancer (16 per cent—similar to the incidence of Duffy et al. and of Winship). He indicates that a certain number of persons would of necessity have had irradiation of the thymus at a time when this procedure was widely used and suggests that a similar correlation might be obtained between malignancy and diphtheria immunization![87]

Therefore the reverse approach is of great importance, namely, to compare the incidence of thyroid carcinoma in children who had been subjected to thymic irradiation with that in a nonirradiated control group. Simpson and Hempelman[73] reviewed 1722 children who had received radiation; they obtained information on 1502; the control group consisted of 1933 nonirradiated siblings. Eleven of the 1502 irradiated children were found to have had thyroid cancer; there was none in the 1933 siblings. These authors also discuss the higher incidence of other tumors, especially leukemias and osteochondromas, in the irradiated children.

Dissenting observations, alluded to above, have been reported by Horn and Ravdin,[41] who obtained no history of previous irradiation in 22 cases of thyroid cancer in young patients, and by Warren et al.:[9] only one out of 23 young patients with thyroid cancer gave a history of irradiation. Uhlman[8] reviewed the problem critically. In his series of 25 thyroid carcinomas, 4 had a history of irradiation of the tonsils. During the same period of 18 years, 2500 children received radiation therapy for enlarged tonsils and for hypertrophic lymphoid tissue of the pharynx; 480 of them, upon examination during a follow-up period of 7 years, yielded no case of thyroid carcinoma. Whereas Uhlman believes that the increase of thyroid cancer in children and adolescents is real, he finds the evidence of a causal relationship with previous irradiation inconclusive. The possible fallacy of drawing conclusions from the incidence of previous irradiation in observed cases of thyroid cancer was referred to above. His comments on the study of Simpson et al. are based on their first report,[72] in which they stated that the incidence of all cancers in the siblings of the irradiated children was high as compared with that in the general population; in their later evaluation[73] no significant difference of incidence of cancers in the siblings and in the general population was found, and none of the siblings had thyroid cancer. Uhlman suggests that enlargement of the thymus and subsequent development of thyroid cancer might have a common (unknown) cause. The statement of Simpson et al.[73] that none of those children who were irradiated, but had no evidence of thymic enlargement (normal mediastinal shadow), had thyroid cancer, might support Uhlman's hypothesis, but the number of cases[81] may be too small for evaluation of this point.

Recently two further follow-up studies of children subjected to irradiation of the thymus have been reported. Latourette and Hodges[55] investigated the fate of 800 patients; the course of 87 per cent (696) could be followed; there was no incidence of thyroid carcinoma over a follow-up period of 17 to 25 years. Similar negative results were reported by Snegireff[78] in a follow-up study of 1131 infants and children having received roentgen radiation to the thymus; there was no thyroid cancer. Both these reports are available only in abstract at this writing, and a detailed comparison with the data of Simpson and Hempelman cannot be made at this time.

From this discussion certain practical conclusions may be presented.

1. In children and adolescents every thyroid nodule should be biopsied.

2. Persisting cervical lymphadenopathy for which an unquestionable cause is not apparent should arouse the suspicion of metastatic thyroid cancer, and a biopsy should be performed.

3. The evidence for an etiologic significance of roentgen ray radiation of the thymus, tonsils and other structures of the upper thorax and neck for the development of thyroid cancer is as yet conflicting. However, this question is losing much of its practical importance inasmuch as radiation therapy of thymic enlargement and of enlarged tonsils has been abandoned in most pediatric clinics, and the widespread and almost indiscriminate use should soon be a matter of the past. Radia-

tion therapy should not be withheld if there is a clear-cut indication such as a radiosensitive malignant lesion.

TREATMENT OF THYROID CANCER. The surgical procedures for operable thyroid cancer are well established. Obviously every thyroid cancer which has not demonstrably metastasized should be operated on. We favor total thyroidectomy rather than hemithyroidectomy: spread across the isthmus, though considered unusual, can occur, and furthermore the possibility of a multicentric origin of the tumor must be considered. If metastases to the lymph nodes of the neck are present, radical neck resection together with thyroidectomy is the procedure used by most surgeons. Whether the operation should be followed by prophylactic roentgen irradiation, or the latter be used only if metastases recur, is not generally agreed upon.

Some more recent developments have permitted of salvage in cases with distant metastases. The use of I^{131} at first appeared limited by the fact that the uptake of I^{131} is low or absent in the majority of cases, because the tumor is too "anaplastic" to exert the iodine-concentrating function of thyroid tissue. This is certainly the case in the type most frequently encountered in children and adolescents, the papillary adenocarcinoma. A small uptake, inadequate for therapeutic effects, may occur, owing to the "mixed" nature of some of these tumors, containing some follicular adenocarcinoma elements. However, exposure of these metastatic tumors to thyrotropic hormone (TSH) may stimulate their differentiation, functional and even structural, and thereby increase significantly their capacity to concentrate iodine. Increased exposure to TSH is best achieved by total thyroidectomy, followed, if the surgical ablation has not been complete, by administration of large doses of I^{131}. Through abolition of the physiologic feed-back mechanism the patient's pituitary gland now continuously secretes large amounts of TSH. Subsequent treatment with large doses of I^{131} now may yield an uptake in the metastases sufficient to obtain a therapeutic effect of radiation. This effect is predicated on the responsiveness of the thyroid cancer to TSH; entirely autonomous cancers will not respond.

Responsiveness of a thyroid cancer to TSH may manifest itself in another way, namely, in increased growth of the cancer under stimulation by TSH. This undesirable effect will be acceptable if at the same time the metastasis can be made to take up I^{131} and thereby subjected to adequate radiation. If this effect of induced hypothyroidism is not achieved, it is best to attempt suppression of growth of the metastasis by administration of thyroid hormone to tolerance, thereby suppressing endogenous TSH secretion. A more detailed discussion of the difficult problem of steering the course between the devil and the deep blue sea is beyond the scope of this review.

TUMORS OF THE PARATHYROID GLANDS

Tumors of the parathyroid glands are rare during infancy and childhood. Some concept of incidence may be derived from the experience at the Mayo Clinic. Of 307 cases of surgically proved primary hyperparathyroidism, the youngest patient was 11 years of age.[68] There appears to be an increased incidence during adolescence. Both primary hyperplasia and tumors of the parathyroid glands result in overproduction of parathyroid hormone and in indistinguishable clinical manifestations. There have been approximately two dozen instances of carcinoma of the parathyroid gland in adults, but none have been reported in children. In adults approximately 82 per cent of patients with primary hyperparathyroidism have a single adenoma, 4 per cent have multiple adenomas, and 8 per cent have primary hyperplasia.[105] Instances of single adenomas and primary hyperplasia of the parathyroid glands have been reported in infants and children, but the number of published cases is too small to compare the relative incidence with that known for adults.[33] Parathyroid adenomas have been reported in more than one member of a family, and the evidence suggests an autosomal dominant type of inheritance.[43] The youngest patient with a familial history of the disorder was 14 years, and multiple adenomas appear to be more common in this group.[77] Some of the reported instances of hyperparathyroidism in children were not surgically explored, and the pathologic findings are not known.

The *clinical manifestations* are protean, and the initial complaints may be primarily referable to the gastrointestinal, renal, osseous or central nervous system. Usually there is more than one affected system. Symptoms may begin during the neonatal period or not appear until later in childhood. Anorexia, failure to thrive and growth failure are usually the predominant symptoms in infancy. Weakness, hypotonia, easy fatigability, vomiting and lethargy are common. Constipation is almost always present, and paralytic ileus may occur. Fever and leukocytosis occasionally are prominent symptoms.

Polydipsia and polyuria are characteristic symptoms. The polyuria is usually assumed to result as a consequence of structural damage to the kidney inflicted by the hypercalcemia. However, recent studies suggest that diminished tubular function results in diminished reabsorption of water in the absence of anatomic changes.[10] In spite of inability to elaborate a urine hypertonic to serum, the nonprotein nitrogen is usually normal early in the disease.[36] It has been suggested that these changes may be the result of a direct effect of parathyroid hormone.[10] As the disease progresses there is deposition of calcium in the renal parenchyma resulting in nephrocalcinosis. Renal function is progressively diminished and is followed by uremia, hypertension, and a return

to normal or above normal of serum phosphate levels. Renal calculi should always suggest the possibility of hyperparathyroidism and are one of the most common presenting signs in adults with this disorder. Renal calculi are rare in young children with hyperparathyroidism, but have been reported more frequently in adolescents.

In children the most common presenting complaints are those referable to the skeleton such as knock-knees, bone pain, tenderness of the extremities, backache, limping, deformities and pathologic fractures.[17, 66, 104]

Central nervous system manifestations such as apathy, headaches, nuchal stiffness, convulsions, coma and mental deterioration have all been reported in children.[33]

Adults with primary hyperparathyroidism show a highly significant incidence of peptic ulcers, but there has been only one instance of this combination reported in a child.[85] The mechanism of this association is not understood. Other rare presenting complaints in children have been ectodermal dysplasia[68] and a lump in the neck. Recurrent pancreatitis with hyperparathyroidism has been reported in adults.

Laboratory Studies. Hypercalcemia and hypophosphatemia are the most characteristic laboratory findings. The alkaline phosphatase activity may be normal or increased, depending upon the degree of osseous involvement. However, even in children with severe osseous disease the alkaline phosphatase may be normal or only moderately elevated. The blood urea nitrogen is usually normal, but may show moderate elevation. Hypomagnesemia has recently been reported in association with primary hyperparathyroidism.[1, 33]

Urinalysis may show a low specific gravity, proteinuria and casts. The calcium content of the urine is increased and can be measured after the patient has been fed a low calcium diet for three days. Roentgenograms may reveal generalized rarefaction of the bones, subperiosteal resorption of bone, absent lamina dura, fractures and deformities. Cysts and tumors are seen only rarely in children. Rickets-like changes at the ends of the long bones have been observed in young children.[104] Nephrocalcinosis and/or renal calculi are occasionally demonstrated. The location of a parathyroid adenoma may be determined roentgenologically by the demonstration of tracheal or esophageal deviation.

Differential Diagnosis. Other causes of hypercalcemia must be considered in the differential diagnosis. Currently, idiopathic hypercalcemia of infancy is probably the most common cause of hypercalcemia. The condition is readily differentiated from primary hyperparathyroidism by demonstration of a normal or slightly elevated serum phosphorus level. Roentgenographically the increased density of the bones of idiopathic hypercalcemia contrasts strikingly with the rarefaction of primary hyperparathyroidism. Hypervitaminosis D can be

eliminated by careful history taking and by demonstration of increased density of bone. Children with hypophosphatasia often show hypercalcemia. The level of serum alkaline phosphatase activity is low, the serum phosphorus level is normal, and the roentgenograms of the bones may show complete disappearance of the zone of provisional calcification and lack of calcification of metaphysial bone.

Secondary hyperactivity of the parathyroid glands is commonly observed in chronic renal disease. The osseous changes and urinary findings may suggest primary hyperparathyroidism. However, the serum phosphorus level is usually elevated or normal, but never low, and the serum calcium level is normal or low, but never elevated.

TREATMENT. Exploration of the parathyroid glands is indicated in all instances in which the diagnosis is clinically established. All the glands should be inspected, and any existing parathyroid adenoma should be removed. In instances of diffuse hyperplasia of the parathyroid glands a subtotal parathyroidectomy is indicated. The serum calcium must be measured postoperatively and the patient observed for the development of tetany, since hypocalcemia may follow removal of a functioning tumor. Intravenous calcium gluconate may be required postoperatively.

Clinical and radiographic improvement in successfully treated patients is dramatic.

TUMORS OF THE ADRENAL CORTEX

Functioning tumors of the adrenal cortex may be divided into distinct categories, depending upon the predominant hormone secreted. Tumors of the adrenal cortex may secrete primarily androgens, estrogens, hydrocortisone (cortisol) or aldosterone. In each instance a characteristic clinical pattern develops. It is not uncommon to find "mixed" tumors which secrete more than one adrenal steroid and give rise to more complex clinical manifestations.

Virilizing Adrenocortical Tumors

Tumors of the adrenal cortex which secrete predominantly excessive amounts of androgenic steroids result in precocious pseudopuberty (macrogenitosomia praecox) in the male and in masculinization of the female. In the *male* the main clinical manifestations are those of premature isosexual development: namely, early signs of masculinization such as enlargement of the penis, scrotum and prostate, appearance of pubic hair and development of acne and a deep voice. There is accelerated linear growth, the muscles are well developed, and the bone age is advanced for the chronologic age.

Symptoms may develop any time after birth. Although the penis is large, testes are relatively small. This is in contrast to true precocious puberty, in which both the testes and penis are enlarged. The clinical manifestations are indistinguishable from those produced by virilizing adrenal cortical hyperplasia. A tumor may be suspected by palpation of a mass or may be suggested by displacement of the adjacent kidney as demonstrated by pyelography.

In the *female* virilizing adrenocortical tumors result in symptoms of heterosexual precocity. Virilization beginning postnatally in a girl who was previously completely normal is almost always due to an adrenal tumor. Wilkins has studied a girl with adrenal hyperplasia who began to virilize at five years of age.[96] The usual manifestations of virilizing adrenal tumors are development of pubic and axillary hair, appearance of acne, deepening of the voice and enlargement of the clitoris. Osseous maturation is advanced. An adrenal adenoma has been reported on a few occasions to be the cause of hirsutism which began in adolescence and was unaccompanied by other evidence of virilization.[44, 52]

In either sex the urinary 17-ketosteroids are elevated both in patients with adrenal cortical tumors and with virilizing adrenal hyperplasia; however, very high values (often associated with a disproportionate increase in the beta fraction) favor the diagnosis of a neoplasm. Large amounts of urinary pregnanetriol are highly suggestive of virilizing hyperplasia.

The most valuable *differential procedure* consists in a therapeutic test with a corticosteroid. Cortisone quickly suppresses excretion of urinary 17-ketosteroids in patients with congenital adrenal hyperplasia, but not in those with a virilizing tumor. Cortisone, by inhibiting secretion of corticotropin, reduces the abnormal stimulation of the adrenals in patients with hyperplasia, whereas adrenal cortical tumors are not subject to pituitary regulation.[96]

A tumor may be palpable; in the absence of such finding the presence of a tumor is sometimes evidenced by changes in the pyelogram, such as in dislocation of the kidney. The tumor can usually be visualized on roentgen films after retroperitoneal pneumography.

The *treatment* is surgical, and a transperitoneal approach is usually recommended. Some of these neoplasms are highly malignant and metastasize widely, but cure with regression of the masculinizing features may follow removal of less malignant encapsulated tumors. A neoplasm of one adrenal may be responsible for atrophy of the contralateral one, owing to excessive production of cortical hormones by the tumor and suppression of the normal gland. Consequently adrenal insufficiency may follow surgical removal of the tumor. In order to avoid this, intensive preoperative and postoperative treatment with cortisone and hydrocortisone is indicated.

Cushing's Syndrome

The clinical pattern of Cushing's syndrome is the result of hyperfunction of the adrenal cortex. When Harvey Cushing described the entity in 1932, he thought it was caused by a basophilic adenoma of the pituitary gland, and excessive secretion of adrenocorticotropin was implied. In many instances such an adenoma cannot be found at necropsy, and there is evidence that the changes in the pituitary may be secondary to prolonged elevation of corticosteroid levels. Prolonged administration of corticotropin or hydrocortisone or its analogues results in a clinical pattern similar to the spontaneous disorder. Cushing's syndrome may result from adrenal cortical tumors or from bilateral adrenal hyperplasia. Whether the adrenal hyperplasia is primarily a pituitary, adrenal or hypothalamic disorder is unsettled at present.[45, 63]

Cushing's syndrome is not common in young adults and is rare in children. Bilateral adrenal hyperplasia and benign adrenal adenoma as a cause of the disorder are especially rare in children under 10 years of age. Thus infants and young children with Cushing's syndrome must be assumed to be harboring an adrenocortical carcinoma until proved otherwise.[5, 28, 30, 31, 53, 57, 65, 69, 80, 92] An excess of hydrocortisone is essential for the development of this syndrome, although there is usually a mixed form of hypercorticalism. Thus, in addition to overproduction of the carbohydrate-regulating hormone, there may be increased secretion of androgens and estrogens. According to the prevalence of a particular hormone, the clinical pattern may vary, and intermediate forms between the adrenogenital and Cushing's syndrome may be manifest. High levels of aldosterone excretion have been observed in several cases.

Symptoms may begin in the neonatal period or any time thereafter. In this form of adrenocortical hyperfunction, obesity of the "buffalo type" and hypertension are outstanding symptoms. The accumulation of fat on the cheeks, chin and upper parts of the trunk and a relative lack of fat on the extremities result in a characteristic appearance. Stunting of growth is common, and in spite of the monstrous appearance, such patients are not markedly overweight. Hypertrichosis on the face, trunk and in the pubic region is common. The skin is plethoric, and the cheeks, in particular, are intensely red. Acne is a frequent finding even in infants, but purplish striae on the hips, abdomen and thighs are seen mainly in older children. The voice may become deep and coarse. In girls the clitoris is generally, but not invariably, enlarged. The breasts occasionally develop precociously, and menstruation begins at an early age. Thus signs of abnormal masculinization and feminization may be seen simultaneously in such girls. In boys the genitals appear normal. The blood pressure is elevated; the heart is often

enlarged; and cerebral hemorrhage may occur. Mentality is initially normal, but as the disease progresses the children frequently become listless, apathetic and dull.

Laboratory Data. The red blood cell count and the hemoglobin level are usually in the range of high normal values, and there is usually an eosinopenia. The blood sugar level may be normal or high, and there may be glycosuria. The plasma electrolyte pattern is sometimes disturbed, and high concentration of sodium and bicarbonate and a decrease in potassium may be present. Patients with Cushing's syndrome excrete increased amounts of 17-hydroxycorticosteroids in the urine. These levels may fluctuate from day to day, and repeated determinations may be required to establish the diagnosis.[4] The urinary output of 17-ketosteroids may be increased, and very high levels suggest a diagnosis of carcinoma.[25] Urinary estrogen excretion may also be elevated.[93] Ossification may be normal or advanced for the patient's age. Osteoporosis is frequent, and spontaneous fractures may occur.[74] The responsiveness of adrenal corticoids to corticotropin stimulation and to 9α-fluorohydrocortisone suppression has been used to differentiate instances of adrenal tumors from adrenal hyperplasia. In general, patients with adrenal hyperplasia show an increased adrenal responsiveness to corticotropin and marked suppression with 9α-fluorohydrocortisone. However, the responsiveness has not been sufficiently investigated in children, and even in adults it cannot be relied upon to differentiate hyperplasia from malignant tumor.[47, 69]

Treatment. All children with Cushing's syndrome should be surgically explored to rule out a tumor. A transperitoneal approach is usually suggested.[95] If an adrenal tumor is present, excellent therapeutic results can be achieved by its removal. Adrenal cortical carcinomas frequently metastasize, especially to the liver and lungs, and the prognosis may be unfavorable in spite of their removal. The contralateral adrenal is usually atrophic, and replacement therapy with cortisone and adrenal stimulation with corticotropin are critical adjuvants in the preoperative and postoperative management of the patient. Benign cortical adenomas are occasionally bilateral. In such cases the treatment of choice is subtotal adrenalectomy. For patients with bilateral adrenal hyperplasia, complete adrenalectomy is recommended. Replacement therapy directed at the prevention of acute adrenal failure must be given scrupulous attention.[58]

Feminizing Adrenocortical Tumors

In Males. Adrenal cortical tumors which secrete estrogens predominantly result in feminization in the male. Thirty-five males with feminizing adrenal tumors have been reported in the world literature,[103]

the youngest patient being that of Wilkins.[94] In this patient gynecomastia developed during infancy, and the breasts were well developed at two years of age. Growth and development were otherwise normal. At five years of age, after removal of an encapsulated adenoma of the adrenal cortex, there was a gradual decrease in the size of the breasts. In the majority of adults the manifestations include gynecomastia, testicular atrophy and loss of libido. A palpable tumor was usually present at the time when medical advice was sought. Approximately 75 per cent of the tumors have been carcinomas and the remainder adenomas. The only consistent laboratory finding has been an elevated urinary estrogen level. Treatment consists in prompt surgical removal of the tumor.

In Females. Adrenal feminizing tumors in girls usually are accompanied by clinical evidence of Cushing's syndrome (see above). Snaith[76] recently reported a unique instance of a 5½-year-old girl with isosexual precocity without evidence of Cushing's syndrome. An abnormally elevated urinary 17-ketosteroid level led to the diagnosis. An encapsulated adrenocortical tumor with "anaplastic changes but no definite evidence of malignancy" was found at operation.

Primary Aldosteronism

Conn,[13, 14] in 1955, was the first to recognize the syndrome produced by excessive aldosterone secretion in a patient who was subsequently found to have elevated levels of urinary aldosterone. At operation an adrenal cortical adenoma was found, and its removal resulted in spectacular clinical improvement. Excessive secretion of aldosterone as a primary disorder of the adrenal cortex due to hyperplasia or a tumor is now known as primary aldosteronism. This condition is to be distinguished from that of increased levels of aldosterone seen in many common disorders such as nephrosis, congestive cardiac failure, cirrhosis of the liver and during dietary restriction of sodium.[83] This latter group is known as *secondary* aldosteronism.

The clinical manifestations of primary aldosteronism consist in muscular weakness simulating periodic paralysis, polyuria, polydipsia, inability to concentrate urine and hypertension. Intermittent paresthesias and tetany may be present. There is no evidence of Cushing's syndrome, and the majority of patients do not have edema.[27]

The urine is persistently alkaline, the specific gravity is low and unresponsive to Pitressin, and there is mild proteinuria. The serum pH, carbon dioxide content and sodium concentration are elevated, and the potassium level is decreased. Serum calcium levels, urinary 17-ketosteroids and 17-hydroxycorticoids are normal, but urinary aldosterone levels are elevated. The severe muscular weakness is the result of the

low serum levels of potassium. The urinary findings are attributed to "clear-cell nephrosis," a lesion characteristic of chronic hypokalemia.

Since the original report by Conn in 1955 there have been many additional instances reported.[16, 38] In the majority of cases a benign adrenal cortical adenoma was found, but in a few instances an adrenocortical cancer or bilateral adrenal hyperplasia was the cause of the increased aldosterone secretion. The few instances reported in children or adolescents thus far have been found to have bilateral adrenal hyperplasia.[40, 88, 89] One child with polydipsia and polyuria since early childhood also had moderate growth failure.

TUMORS OF THE ADRENAL MEDULLA

Pheochromocytoma

Tumors consisting of chromaffin cells which produce large amounts of epinephrine and norepinephrine are called "pheochromocytomas." Their size varies from the size of a cherry to that of a grapefruit, and they occur more often on the right side than on the left.[11, 75] Less than 5 per cent of the reported cases have been in children. In about 25 per cent of affected children there are bilateral tumors, and in about 15 per cent active tumors have been found outside the adrenal gland. In some instances these tumors occur both in the adrenal and in an extra-adrenal site in the same patient. Pheochromocytomas may occur in more than one member of a family, and in such instances the tumors are frequently bilateral.[11] Other neural disorders such as neurofibroma, aganglionic megacolon and megaloureter have been reported in association with these tumors.[17]

The *clinical manifestations* are due to the excess of circulating epinephrine and norepinephrine. The variability of the clinical manifestations in different patients is explained on the basis of the varying proportions of these two substances secreted by different tumors.[54, 90] All affected patients have hypertension at some time. Paroxysmal hypertension may occur and has been thought to be pathognomonic; however, most often the hypertension is sustained, especially in children. When the hypertension is paroxysmal, the attacks are usually infrequent at first, but become more frequent and eventually may be replaced by a continuous hypertensive state. During attacks the patient complains of headache, palpitation and pallor, and vomiting and sweating are noticed. Between attacks of hypertension the patient may be free of symptoms.

In severe cases precordial pains radiate into the arms, and pulmonary edema and cardiac and hepatic enlargement may develop. Central nervous system manifestations such as convulsions, cerebral thrombosis and intracranial hemorrhage have been reported in children. The child has a good appetite, but does not gain weight, and severe cachexia

may develop.[11] Polyuria and polydipsia may be sufficiently severe to suggest diabetes insipidus.[82] Growth failure may be striking.[18, 39] The blood pressure may range from 180 to 260 systolic and 120 to 210 diastolic, and the heart may be enlarged. Ophthalmoscopic examination may reveal papilledema, hemorrhages, exudate and arterial constriction.[97]

Laboratory Data. The urine contains albumin and a few casts. When the predominant catechol amine secreted by the tumor is epinephrine, hyperglycemia and hypermetabolism may occur. In such patients, glycosuria, a diabetic glucose tolerance curve and a basal metabolism rate as high as plus 50 or 60 may be demonstrated.

The most direct and specific test for the detection of pheochromocytomas is the measurement of urinary excretion or of blood levels of catechol amines.[54, 90] Norepinephrine is increased in the urine in all patients, but epinephrine is not invariably increased. There is a direct relation between the proportion of these substances in the tumor and in the urine. The elegant technique of selective venous catheterization with analysis of the blood for concentration of catechol amines at different sites has successfully been used by von Euler[90] to localize tumors and by Cone[12] to prove that a mass in the neck was a functionally active pheochromocytoma.

Diagnosis. A variety of drugs may be used diagnostically, but the two most useful ones are histamine and phentolamine (Regitine).[54, 90] If the hypertension is paroxysmal, histamine administered intravenously stimulates release of epinephrine and norepinephrine, thus provoking an attack similar to those occurring spontaneously. When the hypertension is continuous, phentolamine may be used as an adrenolytic agent. Three to 5 mg. of this substance administered fairly rapidly by the intravenous route will result in a prompt fall of more than 35 mm. of systolic pressure and of 25 mm. of diastolic pressure if a pheochromocytoma is present. Falsely positive results may be obtained if the patient is taking sedatives or narcotic drugs, and falsely negative ones in patients taking antihypertensive drugs.

In the *differential diagnosis* the usual causes of hypertension must be considered, such as renal disease, coarctation of the aorta, acrodynia, hyperthyroidism, Cushing's syndrome, congenital adrenal hyperplasia and essential hypertension. If the hypertension is paroxysmal, the diagnosis of familial autonomic dysfunction must be ruled out; a number of children with this entity have been explored for pheochromocytoma.[2] There have been a few instances of hypertension and increased excretion of catechol amines produced by neuroblastomas.[59]

Treatment. Localization of the tumor before operation is highly desirable, but is often difficult. Occasionally it can be discovered by palpation. Pyelography, presacral injection of pure carbon dioxide, or

aortography[79] may reveal the location of the tumor. Selective venous catheterization as mentioned above is a highly specialized procedure that has proved useful. Removal of the tumor usually results in a cure. The operation is not without danger, because an extreme rise of blood pressure may result from massive discharge of hormone during operative manipulation. Another danger is that of shock from a precipitous drop of blood pressure during operation or within the first 48 postoperative hours. These dangers can now be coped with by the use of phentolamine before and during operation to prevent hypertensive crises and of norepinephrine to prevent shock.

Utmost vigilance is required postoperatively. The urinary excretion of catechol amines should be determined after operation as a measure of the completeness of the surgical procedure. Cone[12] reported the recurrence of a pheochromocytoma in the neck of a child 2¼ years after the successful removal of a right suprarenal pheochromocytoma. Harrison, Gardner and Dammin[35] reported an instance of persistent hypertension after removal of a pheochromocytoma. Normal levels of catechol amines postoperatively clearly indicated lack of residual pheochromocytoma. Further studies led to the establishment of unilateral renal disease as the cause of the persistent hypertension.

TUMORS OF THE OVARY

Only functional, hormone-secreting tumors will be considered in this review. Other ovarian tumors are dealt with elsewhere (p. 491).

Estrogen-Producing Tumors

These tumors cause isosexual precocious pseudopuberty.* Development of breasts and of pubic hair, and uterine bleeding, cyclic but usually irregular, take place. Growth and epiphysial maturation are advanced. Such tumors have been observed in infants a few months of age, and in older children. These tumors are rare, and while their presence should be suspected in every case of isosexual precocity, other more common causes have to be considered in differential diagnosis.[61, 96] The most frequent cause of such precocious sexual development is true precocious puberty without any demonstrable lesion, also referred to as "con-

* Precocious puberal development is subdivided into two main groups. In true precocious puberty the entire puberal development is anticipated at an early age, including (1) stimulation and maturation of the gonads through action of pituitary gonadotropins (in turn released, in all probability, through hypothalamic neurosecretions), and (2) secretion of sex steroids from the precociously matured gonad in an orderly fashion, causing precocious development of secondary sex characteristics. In precocious pseudopuberty the secondary sex characteristics develop precociously, owing to sex steroid production in tumors or in the adrenals; the gonads do not participate in the development.[61]

stitutional" precocious puberty. This has to be regarded as a normal puberty occurring at an abnormally early age. True precocious puberty also occurs as a result of certain brain lesions; a rare type of true precocious puberty is associated with polyostotic fibrous dysplasia of bones (Albright's syndrome). Precocious puberty of the latter two types can usually be recognized from the characteristic manifestations of the underlying disease. The diagnosis of constitutional precocious puberty, the most common of all, requires exclusion of all other causes, particularly and most seriously that of an estrogen-producing tumor. The latter is almost always palpable either by abdominal or pelvic palpation; in many instances the pelvic examination has to be performed under anesthesia. In the absence of a palpable mass the presence of a tumor is unlikely. Unfortunately, in many cases, hormone assays have not been reported. From available evidence it would appear that in cases of true precocious puberty, "constitutional" or due to cerebral lesions, the urinary estrogen excretion varies over the range that is normal for adult women of the childbearing age. Estrogen excretion in cases of ovarian tumors has been found much higher than that of normal adults. In case of doubt, an exploratory operation will be necessary. Following these general statements regarding estrogen-producing ovarian tumors, we give a brief outline of the types of tumors in question.

Granulosa Cell Tumor. (See also p. 497.) This tumor is of low grade malignancy; therefore surgical removal of the tumor brings about a permanent cure in most instances, but some children have died from metastases (6 per cent). Occasionally the tumor is bilateral, and the occurrence of a tumor in the second ovary after successful removal of the first has been observed.[96] The youngest patient reported was 14 weeks old.[15]

Teratoma. (See also p. 491.) In rare instances, teratomas of the ovary give rise to precocious pseudopuberty, indistinguishable from that observed in granulosa cell tumors.[34]

Choriocarcinoma (Chorio-epithelioma). (See also p. 498.) When the ovary is the primary site of choriocarcinoma (as is the case in children), this tumor evidently arises in, or as part of, a teratoid tumor. It is highly malignant and metastasizes early. Precocious pseudopuberty develops in children, clinically indistinguishable from that induced by the other estrogen-producing tumors. The hormone excretion pattern is characteristic, inasmuch as, in addition to the high estrogen excretion, there is excretion of large amounts of chorionic gonadotropin. Presence of this hormone will establish the diagnosis, which otherwise is only made upon histologic examination at operation. The estrogen and gonadotropin excretion usually disappears after operative removal of

the tumor, to return when metastases develop. Prognosis is poor. A folic acid antagonist (Methotrexate) has been used with promising results in cases of choriocarcinoma of the uterus,[37] but has been ineffective in primary choriocarcinoma of the testis. It will be important to try this medication in metastatic choriocarcinoma of the ovary.

Dysgerminoma. (See also p. 498.) These tumors, believed to originate from undifferentiated cells of the gonad, are usually found to be hormonally inactive; they are sometimes associated with female pseudohermaphroditism, but are thought to be not causally related to this condition because removal of the tumor does not modify it. Ewing[22] states that these tumors are sometimes associated with teratoma and chorio-epithelioma of the ovary.[22]

Three cases are on record in which a dsygerminoma was associated with precocious pseudopuberty. The question whether the dysgerminoma itself was responsible for the abnormal hormone production has been raised; in the case of Tietze, the possibility that elements other than the dysgerminoma might have been present, but not discovered in the sections (granulosa cells? adrenal cells?), has been discussed. In Hain's[32] case, hormone assays were performed and a high excretion of chorionic gonadotropin was found. The author found four other cases of this tumor in the literature, associated with high chorionic gonadotropin excretion. This finding is, in our opinion, highly suggestive of the presence of chorio-epithelioma elements, even though they were not discovered on histologic examination. The observation of Ewing, quoted above, of such occurrence adds weight to our suspicion. The rare occurrence of sexual precocity in dysgerminoma would then be due to the presence of other tumor elements, of a type known to be hormone producing and associated with precocious pseudopuberty.

Ovarian Cysts. (See also p. 495.) In rare instances of precocious sexual development, including uterine bleeding, unilateral ovarian follicle cysts have been found. The cysts are large enough to present themselves as ovarian tumors on pelvic (rectal) examination. After surgical extirpation of the involved ovary cessation of menstruation has been observed. Recurrence of the precocity has been reported;[26] in another case there was no recurrence during a postoperative observation period of four years.[51] No girl has been followed up long enough, up to the time of normal puberty, to permit a statement about the further development of these patients. In the few cases in which hormone assays were performed, estrogen excretion, though high for the respective early age, did not exceed normal adult values. Small amounts of gonadotropic hormone were demonstrable in one completely studied patient aged 4 years.[7]

It is most likely that these patients represent cases of true precocious puberty, constitutional, or due to cerebral lesions, or associated with polyostotic fibrous dysplasia (Albright's syndrome),[67] in whom for reasons unknown one ovary responds excessively with cyst formation. If this is true of all cases, resumption of the precocious development after temporary regression should be expected; as mentioned above, information on this point is as yet inadequate.

Extirpation of these large cysts is indicated; they are unilateral, and the surgical procedure almost always will involve extirpation of the entire ovary. In the hypothetical case of bilateral involvement a more conservative procedure (drainage of the cyst, extirpation of the wall) would have to be considered. *In true precocious puberty, multiple small follicle cysts may be present bilaterally;* they are of course not palpable on pelvic examination, but may be found if, because the diagnosis is in doubt, an exploratory operation is performed. There is no reason for removing such ovaries.

Androgen-Producing Tumors

Androgen-producing ovarian tumors in a prepuberal girl cause varying degrees of heterosexual (male) precocity. Advanced height and epiphysial maturation are associated with growth of pubic hair, enlargement of the clitoris and deepening of the voice.

For differential diagnosis, we must consider (*a*) adrenocortical hyperplasia, (*b*) adrenocortical tumors, (*c*) exposure to (exogenous) androgens. Virilizing congenital adrenocortical hyperplasia is characterized by the presence of a urogenital sinus resulting from the action of androgens upon the structures involved, in intrauterine life. A urogenital sinus will obviously not be present in any virilizing lesion developing after birth because the urogenital septum, once developed, does not regress.

The heterosexual precocious pseudopuberty and virilization resulting from adrenocortical hyperplasia developed in postfetal life, or from tumors of the adrenal cortex or of the ovary, are indistinguishable clinically.

Hormone Excretion. In congenital virilizing adrenocortical hyperplasia the 17-ketosteroid excretion is always high as compared with the normal ranges for the age level, but not necessarily higher than normal adult levels. In addition, there is always an increased excretion of pregnanetriol. After stimulation with ACTH both 17-ketosteroid and pregnanetriol excretion increases appreciably; contrariwise, the excretion is readily suppressed by administration of cortisone and related steroids. The adrenocortical tumors usually show a much higher level of urinary

17-ketosteroids (often with a disproportionately high level of the beta fraction), but there is no pregnanetriol excretion. Generally, ACTH fails to increase, and cortisone equally fails to suppress, 17-ketosteroid excretion significantly in cases of adrenocortical tumor, but exceptions have been reported, indicating that some adrenocortical tumors are not autonomous.

As to the virilizing ovarian tumors, much less information is available, because these tumors are rare; unfortunately, some cases are not studied completely. In adrenal rest tumors (masculinovoblastomas) the 17-ketosteroid excretion usually follows the pattern seen in adrenocortical tumors; in some instances high pregnanediol excretion has been reported, and this, together with the changes in the endometrium, has suggested the origin of the tumor from lutein tissue (see below).

In cases of arrhenoblastoma, in adolescents, the 17-ketosteroid excretion is often only moderately, if at all, increased. The reason for the discrepancy of marked virilization, and absent or only moderate increase of 17-ketosteroid excretion is not clear. It should be remembered that the total neutral 17-ketosteroids consist of a mixture of androgenically active, and of inert, steroids; only by chromatographic analysis can the ratio of the individual components be determined. It is hoped that in due time such studies will be performed on a sufficient number of cases to permit an evaluation.

Arrhenoblastoma. Of the masculinizing ovarian tumors, arrhenoblastoma and hilar cell (Leydig cell) tumor have not as yet been observed in prepuberal girls. Arrhenoblastoma has been described in adolescent girls, past the age of 15.[23, 24]

Adrenal Rest Tumor (Masculinovoblastoma, Luteoma). Histologically, these tumors are characterized by large lipid-containing cells, evidently secreting androgens. The origin from adrenocortical tissue, not infrequently found in the ovary or the broad ligament, appears probable, but morphologically the origin from lutein tissue cannot be excluded. Nor is it certain that the genesis of all these tumors is identical. In a case reported by Twombly,[86] in a girl 15 years of age, the "decidual reaction" of the endometrium suggested that the tumor was functioning as a corpus luteum. However, she also exhibited virilization and moderately elevated urinary 17-ketosteroid excretion. In a girl aged six, we observed heterosexual (male) precocious pseudopuberty and moderately elevated 17-ketosteroid excretion.[62] In other cases the 17-ketosteroid excretion has been found very high.

In the presence of a noncongenital heterosexual (male) precocious pseudopuberty, very high excretion levels of 17-ketosteroids, responding neither to stimulation by ACTH nor to suppression by cortisone, are indicative of an adrenal tumor or, presumably, of an adrenal rest tumor

of the ovary. The ovarian tumor will usually be palpable on pelvic examination; the adrenal tumor can be visualized by retroperitoneal pneumography. In either instance only a positive finding is conclusive. In the case of the six-year-old girl mentioned above, the result of a rectal examination under anesthesia was not considered conclusive, but only strongly suggestive by the gynecologist. In case of doubt, or in the absence of conclusive findings, an exploratory operation must be performed. Because it is the simpler procedure, abdominal exploration should be done first. If the findings in the ovaries are negative, an attempt can be made at palpating the adrenals from the abdominal cavity; but it may be necessary to explore the adrenals from a dorsal (kidney) incision in a second operation.

Adrenal Rest Tumors in Cushing's Syndrome. In rare instances these tumors are associated with Cushing's syndrome; one such case occurred in an adolescent girl aged 13.[50]

TUMORS OF THE TESTIS

The principal hormone-secreting tumor of the testis in children is the interstitial cell tumor (see also p. 502). It is derived from the interstitial cells of Leydig. These cells are sparse before puberty, and tumors derived from them are rare. Approximately 24 cases in children have been reported since Sacchi first described an instance in a 9-year-old boy in 1895.[3, 19, 48, 64, 70] These tumors produce androgenic hormone which results in precocious pseudopuberty.

The first changes, enlargement of the penis and development of pubic hair, are seen usually between the ages of four and six years. Axillary and facial hair appear later, but long before the usual age of puberty. Hypertrichosis of the chest and extremities may also be present. The boys grow rapidly, they gain in weight and are muscular and strong. The voice becomes deep. The blood pressure is usually within normal limits. The tumor of the testis is usually palpable when the patient first seeks medical advice. The prostate gland may also be enlarged, and erections are common. Roentgenograms reveal precocious osseous development, and the 17-ketosteroids in the urine may be slightly or markedly increased.

Treatment consists in surgical removal of the testis which contains the tumor. In one instance the tumor was found in the tunica vaginalis completely separate from the testis.[3] A partial disappearance of the signs of precocity has been observed in some patients. Progression of virilization always ceases after the tumor has been removed. One instance of a bilateral tumor has been recorded, but there is reason to believe that this represented hyperplastic ectopic adrenal tissue.[81] Leydig cell tumors are usually benign.

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2600 N. Lawrence St.
Philadelphia 33, Pa. (Dr. Di George)

LEUKEMIA AND LYMPHOMA IN CHILDREN

M. LOIS MURPHY, M.D.

The leukemias and the lymphomas constitute the major forms of neoplastic disease in children (Fig. 103). Acute leukemia in childhood was discussed by Mila Pierce[46] in the May, 1957, *Pediatric Clinics of North America*. Several complex systems of classifying these disorders have been proposed, but the simplest and most useful one in our experience is as follows:

Acute leukemia: It is difficult to separate the truly blastic stem cell leukemias into types, but when accompanying promyelocytes, lymphocytes or monocytes make this possible, differentiation should be attempted.

Chronic granulocytic leukemia: This constitutes about 5 per cent of the leukemias in children.

Hodgkin's disease.

Lymphosarcoma, including reticulum cell sarcoma: This often begins as a generalized disease, and may transform into a leukemic phase in advanced stages; occasionally remains localized for long periods.

Because of the hematologic remissions so far produced by chemotherapy in acute leukemia of childhood, it may prove to be the first type of cancer susceptible to prolonged control by chemotherapy. The large number of cases of acute leukemia in children available for study, and the brief span between prenatal life and the fourth year, when the peak incidence of childhood leukemia occurs, may permit the epidemiologist to elucidate factors responsible for the onset of the disease. Research in the causes and the treatment of leukemia has been greatly intensified against what may prove to be the vulnerable spot in the cancer problem.

From the Pediatric and Chemotherapy Services, Memorial Center for Cancer and Allied Diseases, Division of Clinical Chemotherapy, Sloan-Kettering Institute, and the Department of Pediatrics, Cornell University Medical College, New York City.

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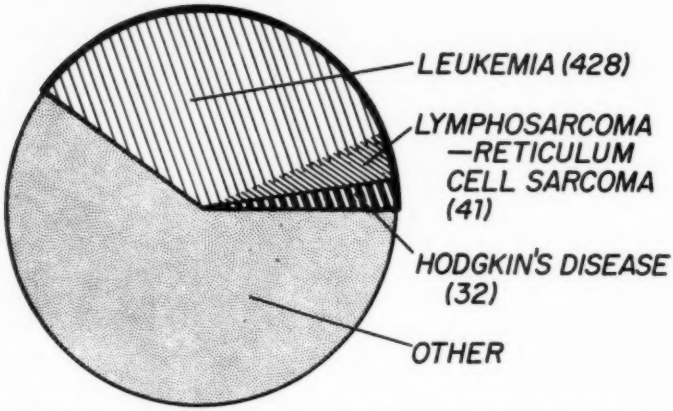


Fig. 103. Distribution of types of neoplastic diseases in children in 1248 consecutive cases seen at Memorial Center 1926–55. Hospital admissions for acute leukemia have increased recently, owing to the availability of therapeutic measures. In recent years, however, the recorded number of cases of leukemia has also increased, but how much of this is due to an increase in leukemia per se is not known.[40] (Information on distribution obtained through the courtesy of Harold Dargeon, M.D.)

It is desirable to establish the correct diagnosis early. This may spare the ailing child—if the correct diagnosis had not been made—from long periods of discomfort that might have been controlled by proper therapy. In leukemia, if treatment is begun early in the relatively asymptomatic child, a satisfactory remission may be induced and the disease controlled for long periods while the child is able to lead a normal life. In Hodgkin's disease and lymphosarcoma, early therapy of localized tumor may prevent dissemination for many years.

ACUTE LEUKEMIA

Clinical Characterization

Acute leukemia may present itself in many ways, and the leukocyte count initially may be as high as 1,000,000 per cubic millimeter or as low as 200. Tivey[59] in his review of the literature found that 40 per cent of children with acute leukemia had normal leukocyte counts in the peripheral blood. Bone marrow aspiration is essential for correct diagnosis. As the disease evolves, anemia and thrombocytopenia occur. The leukemic process infiltrates the lymph nodes, the liver and the spleen, and enlargement of one or more of these structures is common. All tissues or organs may be invaded, including the nervous system, the skin, the kidneys, the cortex and periosteum of the bones, as well as the marrow, the gastrointestional tract and the endocrine glands.

The median age for acute leukemia in children is about four years,[59] although it occurs at all ages. The ratio of males to females is approximately 1.4:1. Pierce[47] has collected 45 acceptable cases of leukemia of the newborn from the literature. The disease appears to have a higher incidence than normal in mongolism.[38]

There does not appear to be a strong family incidence of leukemia.[16] It is rare to have leukemia occur in more than one member of a sibling group, although such instances have been reported.[1] Leukemia has been noted occasionally in identical twins, and fraternal twins may both have the disease.[2] Mothers with acute leukemia may bear healthy children, although there is a case report of acute leukemia in a 9-month-old infant whose mother died of acute leukemia soon after the birth of the child.[18] Mothers of children with congenital leukemia have not had the disease.

The signs and symptoms which leukemia produces in the patient may be divided into two broad groups. The first includes those due to replacement of the bone marrow by leukemic cells; there is decreased production of red cells, platelets or normal granulocytes, resulting in anemia, fatigue, pallor, hemic murmurs, ecchymoses, purpura, petechiae and hemorrhage or decreased resistance to infection. The other signs and symptoms are produced by invasion of leukemic cells into various organs, producing enlarged lymph nodes, mesenteric adenitis, intussusception, intestinal perforation and enlargement of the liver, spleen and kidneys.[55] Infiltration of the nervous system and meninges may give specific motor palsies, a picture of hypothalamic stimulation, headache, vomiting, coma, and death due to increased intracranial pressure. Sullivan[56] has reviewed seven patients with these complications. Infiltrations in the bones may cause local pain, rarefactions, and inability to bear weight with some muscular atrophy.*

Pathologic fractures may occur. These are serious, particularly when the vertebrae are concerned. Infiltrations of the conjunctiva, the skin, the breasts in adolescent girls, the thyroid, the testicles and the kidneys occur with the resultant local disturbances. Splenic enlargement is common, and infarction sometimes occurs. The liver may enlarge, owing to disease, and then shrink after treatment, and this may occur several times; the damaged liver may develop a picture reported as cirrhosis.[15] Hutter et al.[34] have reviewed the histology of the livers of 263 consecutive treated cases of acute leukemia in children who had autopsies at Memorial Center. They observed a high incidence of hepatic fibrosis, most severe in the longer survivors.

* These children may be referred to an orthopedist or poliomyelitis center because of pain in the spine and lower extremities. Sometimes acute leukemia is erroneously diagnosed and treated as rheumatic fever.

Leukemic involvement of the bone marrow may or may not produce pain. The occurrence of severe bone pains may be due to the increased volume of cells in the marrow cavity during exacerbation of the disease, as suggested by the studies of Petrakis.[45] Anemia may contribute to this pain, however, since an increase in hemoglobin by blood transfusions may relieve the pain. Local irradiation with small doses of x-ray may give transient relief of bone pain.

Elevations of serum uric acid levels in the range of 10 mg. per 100 ml. are often found in patients having high leukocyte counts or bulky lymph nodes. In such cases treatment which may produce a rapid fall of the leukocyte count and shrinkage of tumor may cause a rise in serum uric acid and produce renal injury and anuria.[37]

Treatment

It is sometimes wise, even when a definite diagnosis of acute leukemia exists, to obtain consultation, to reassure the family that every possibility is being considered. It is a false sense of kindness, however, to allow parents to go from physician to physician and put the child through numerous diagnostic procedures in the hope of finding a different answer. If a diagnosis is not definite, observation and later repetition of the diagnostic procedures will usually serve to establish the correct diagnosis. The methods useful for the management of acute leukemia are now well established and can be carried out by any competent pediatrician. The leukemic child may be referred to a specialized center early or only after he has become resistant to conventional therapy. When this is done at the outset of the disease, or when the child is resistant to treatment, the parents are grateful if the referring physician selects and contacts such a center, arranges an appointment and informs the center of the details of the child's clinical management.[6]

Treatment includes supportive measures, such as correcting anemia and controlling infection, and specific therapy aimed at suppression of the leukemic processes with consequent return to normal function of hematopoiesis and any other impaired tissue or organ function. The patients and their families understandably require a great deal of support for their emotional and situational problems.

Supportive Measures. *Anemia.* Many children at the time of diagnosis are not anemic and, if the antileukemic therapy is effective, may not have anemia until resistance to treatment occurs. On the other hand, the anemia of the newly diagnosed case of acute leukemia may be of rapid onset and of severe degree. The hemoglobin level may fall by 2 gm. or more daily even in the absence of active bleeding. Syncope

is not unusual. Since the bone marrow is largely replaced, with the absence of erythroid activity the anemic status of the patient cannot be expected to stimulate red cell production. Transfusions of whole blood should be given as indicated during the early stages of treatment to maintain the leukemic child's hemoglobin level in the range of 9 gm. Repeated transfusions should be given over the first few days or weeks to achieve and maintain an acceptable hemoglobin level. Whole blood is usually used, but packed red cells may be indicated for the patient with hemoglobin values of 3 or 4 gm. per 100 ml. If cardiac failure develops, this is usually due to the severe anemia, and transfusions should be continued while the patient is digitalized and given oxygen. In patients with a leukocyte count over 100,000 a blood transfusion may cause a temporary lowering of the count by as much as 50 per cent.

In patients with high leukocyte counts and bulky disease, specific therapy is withheld during the first 24 hours while anemia is being corrected and adequate fluid intake established, so that urine output is good. During the period of response to chemotherapy administration of iron may hasten the rise in hemoglobin level. We avoid administration of folic acid and citrovorum factor. Farber[27] observed that pteroylglutamic acid would exacerbate acute leukemia, and we have observed acute relapses in leukemic children who received an intravenous dose of 0.05 mg. per kilogram of folinic acid (citrovorum factor) in the course of a study.

Infection. The susceptibility of the child with acute leukemia in relapse to intercurrent infection is a major problem and has been examined in detail by Silver et al.[53] The history of one respiratory infection after another, each appearing to respond only temporarily to antibiotics, may be one of the early manifestations of leukemia. The leukemic child with obvious infection or fever should have adequate bacteriologic studies and the proper antibiotic prescribed. In the absence of a known infecting organism, but in the presence of a high fever, the child should receive a broad-spectrum antibiotic along with the antileukemic therapy and attempts to identify the infectious process continued. Many leukemic patients may be in total hematologic relapse without fever, so that the occurrence of high fever must be presumed to be due to a secondary infection. Prophylactic antibiotics are not recommended simply because the leukocyte count is low or the patient is on adrenal corticoids. Identification of a severe infectious process such as septicemia, meningitis, contagious disease or empyema in acute leukemia in relapse is an indication for large doses of adrenal corticosteroids along with the proper antibiotic. As soon as a bone marrow remission is obtained, the adrenal steroid is discontinued, but antibiotic

is given until the infection is controlled. The patient in a remission is usually able to handle the infection as well as a normal person, although one exception is the severe manifestations of varicella which have occurred in the leukemic patient, even while in remission.[60]

Adequate surgical drainage should be used when indicated in infections in the leukemic patient. Occasionally if the patient presents a persistent draining abscess or has ulceration of the hard palate or of the buttocks and if the leukemia is in relapse, x-ray therapy in small doses to these areas may promote healing.

Administration of adrenal steroids and antibiotics over long periods of time and the debilitated state of the patient not responding or resistant to therapy are responsible for persistent moniliasis as well as other fungal and bacterial infections. Nystatin (Mycostatin) for oral or gastrointestinal moniliasis, and amphotericin B (Fungazone) for oral, gastrointestinal or systemic fungi, have been helpful. If the patient is no longer able to develop an adequate systemic response to infection, the effect of these drugs is often brief and unsatisfactory.

If is our policy to avoid intramuscular injections in patients with hemorrhagic diatheses because of the frequent hematomas and their tendency to become secondarily infected. In these cases antibiotics are administered as continuous intravenous infusions which the children accept remarkably well and actually prefer to intramuscular or even occasionally to oral medications.

CHEMOTHERAPY. Drug-induced remissions in the acute leukemias of childhood have rightfully been called one of the most remarkable phenomena of modern medicine. Two categories of drugs, the antimetabolites (the antifolics and 6-mercaptopurine) and the adrenocortical hormones (Table 22), exert separate therapeutic effects.

The principal antimetabolites (Table 22) are the folic acid antagonist Methotrexate (4-amino-N^{10}-methylpteroylglutamic acid) and the purine antagonist Purinethol (6-mercaptopurine). The adrenocortical hormone most widely used is prednisone; other adrenal steroids are available, and the adrenocorticotropic hormone (ACTH) is occasionally used in specific situations in preference to prednisone. At present there is no way of knowing in advance which agent will produce a therapeutic effect. Resistance inevitably develops in a patient who responds initially, even though the dosage of the drug is raised to the point of severe toxicity in the host. Resistance to one type of agent does not preclude a favorable response to another type. Such a patient should be given the opportunity to receive a representative of each type of drug.[12]

TABLE 22. *Principal Chemotherapeutic Agents in Acute Leukemia in Children*

AGENT	COMMON NAME	INDICATIONS	ROUTE OF ADMINISTRATION	DOSE DAILY	MAINTENANCE DOSAGE	TOXICITY (OVERDOSE)	TIME INTERVAL TO OBTAIN RESPONSE	PERCENTAGE OF PATIENTS OBTAINING RESPONSES	APPROXIMATE DURATION OF AVERAGE RESPONSE	CROSS RESISTANCE
				Antimetabolites						
4-amino-N[10]Methyl pteroyl-glutamic acid	Methotrexate (Amethopterin) 2.5-mg. tablets	Low leukocyte count, fairly good clinical condition, and in any patient resistant to Purinethol	Oral	2.5–5.0 mg.	Satisfactory or may be discontinued when remission occurs, resumed when relapse of marrow occurs	Oral and intestinal ulcers, diarrhea, depression normal marrow, bleeding, late-temporary alopecia	2–6 weeks	35–50	7 months	Cross-resistant to antifolics, such as aminopterin (etc.); no cross-resistance to Purinethol or adrenal steroids
		Central nervous system involvement with symptoms of increased intracranial pressure, pleocytosis in cerebrospinal fluid, and bone marrow remission	Intrathecal	0.25 mg./kg. q2 day or 0.5 mg./kg. q 4–5 days (usually 2–3 doses)	Resume if neurologic complication returns	Larger doses may cause convulsions	Few to 24 hours	80–90, meningeal type	5 months	
6-Mercaptopurine	Purinethol (50-mg. tablets)	Low or high leukocyte count, fairly good condition, and any patient resistant to antifolics	Oral	2.5 mg./kg.	Recommended, 2.5 mg./kg. per day	Oral ulcers, ulceration of digestive tract, depression of normal marrow	2 - 6 weeks	50–70	4 months	Cross-resistant to other purine analogues, but not to antifolics or adrenal steroids
				Adrenocorticosteroids and Adrenocorticotropic Hormone						
Δ1,4 pregnadiene 17,21-diol-3,11,20 trione	Prednisone	Severely ill due to disease	Oral	20–100 mg.	Not recommended. Discontinue when remission occurs. Start on antimetabolite when marrow relapses	*IMMEDIATE* Hyperuricemia if disease response is rapid and fluid intake and output poor *DELAYED* Cushing's appearance; sodium retention;* hypokalemia;* elevated blood pressure;* convulsions;* excessive appetite and weight gain; osteoporesis; suppression of intrinsic adrenal function; susceptibility to moniliasis; emotional reactions (rare in children)	Few hours to 1 week for sensitive cases. 3–4 weeks in relatively resistant cases	70–80	6 weeks	Adrenal corticosteroids, but not Purinethol or Methotrexate
	Prednisilone or Adrenocorticotropic hormone	Severely ill plus active bleeding	Continuous intravenous infusion	20–100 mg.						
			Continuous intravenous infusion	25–50 mg.						

* More common with Compounds E or F; or ACTH.

There are various methods under study for the treatment of leukemia, and it is difficult to obtain sufficient patients at one institution for accurate comparative studies. The accelerated program for finding more effective chemotherapeutic agents against cancer promoted by the Cancer Chemotherapy National Service Center of the National Cancer Institute[26] has sponsored the organization of cooperative study groups. These groups collect data on a comparable series of cases, using a specific protocol for patient selection and therapy and standardized criteria of evaluation, and then pool their results. Such a group, Acute Leukemia Cooperative Chemotherapy Study Group A, has been functioning since January, 1956, and now comprises 14 different medical centers. Together they see approximately 170 acute leukemic children each year. They are now using a modification of the criteria for evaluation[39] established by the Clinical Studies Panel of the Cancer Chemotherapy National Service Center.[4] The criteria for rating acute leukemia are divided into four categories designated *A*, bone marrow; *B*, peripheral blood; *C*, physical findings; and *D*, symptoms.

The most satisfactory response to therapy is the complete remission wherein no evidence of disease can be detected in the bone marrow and peripheral blood, and physical findings or symptoms. In failure to achieve a complete remission, partial and symptomatic remissions are recorded.

From the graph in Figure 104 it can be seen that the bone marrow* relapse may occur without changes in the peripheral blood and often without physical signs or symptoms. If the patient is followed up by serial examinations of the marrow at intervals of two to four weeks, marrow relapse is usually the first sign of progression of the disease. On the basis of the marrow findings a subsequent plan of treatment is determined. By this means the patient usually does not become clinically ill, does not require hospitalization, and is able to continue his normal activities until he has developed resistance to the available agents.

Choice of Agents. The majority of children at the time of diagnosis of leukemia are in fairly good condition. One of the antimetabolites therefore is the drug of choice even though improvement in the patient may not begin for about three to eight weeks. The more rapidly acting adrenal corticosteroids are thus saved for some future time in the course when the disease is in severe relapse and a rapid remission is mandatory. For a child who appears to be in critical condition at the time of diagnosis, the adrenal corticosteroids are the initial form of treatment. As soon as a complete remission occurs, prednisone is discontinued. The patient receives no further treatment during remission, but the bone marrow is closely followed, and an antimetabolite is started at the first sign of bone marrow relapse.

* In our clinic the Turkel needle size 16 outer with 18 trephine is used, only the trephine enters the bone and marrow cavity. The trephine is removed and a drop of marrow aspirated through the outer needle with a 2-cc. syringe. It is smeared like a blood smear for staining and examination. The marrow sites are sternum, which we prefer, iliac crest, or spinous processes of the thoracic vertebrae. Repeated punctures of the tibia are not encouraged.

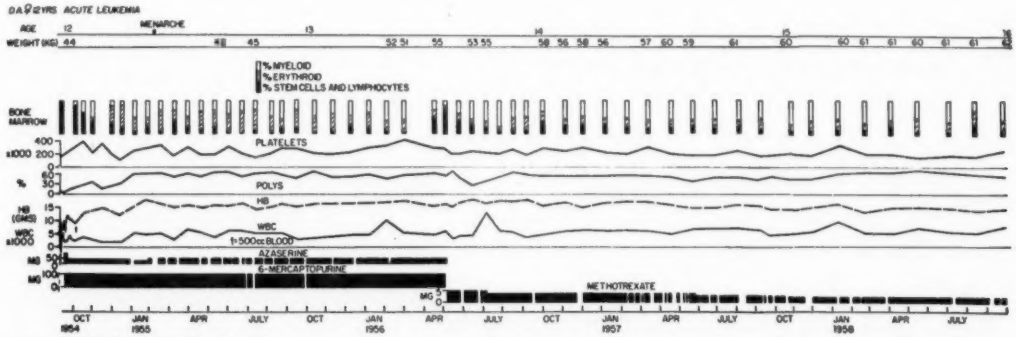


Fig. 104. Acute leukemia.

In August, 1954, a 12-year-old school girl experienced easy fatigue when swimming and climbing stairs. Her hemoglobin level was 5.9 gm. per 100 ml., the total leukocyte count 1500, and an occasional ecchymosis on her lower extremities and slight splenomegaly were found. The bone marrow revealed sheets of blast cells with no normal erythroid or myeloid elements or megakaryocytes. She received blood transfusions and was referred to Memorial Hospital for treatment. Since her hemoglobin count was then 8 gm. per 100 ml., she was treated in the outpatient department.

The course of her disease and the response to treatment and her age and weight are shown. The bone marrow, peripheral blood and physical findings of leukemia disappeared within a few weeks after administration of 6-mercaptopurine and azaserine (O-diazoacetyl-L-serine)[10] was begun, and maintenance therapy was used. Azaserine was discontinued on days when soreness of the mouth developed. After 15 months, in May, 1956, she was found to have a spleen and liver palpable 3 cm. below the costal margin, and a count of the bone marrow aspirate showed 71 per cent blast cells. There were no subjective signs, and the peripheral blood remained essentially unchanged. The chemotherapy was changed to Methotrexate. Again there was a prompt response in the bone marrow toward normal. The patient did not exhibit subjective symptoms.

The therapy and hematologic status since that time, up to and including November, 1958, are shown, and Methotrexate is being continued. The patient remains in good health. She has not been hospitalized since her diagnosis, and goes to school regularly. Menarche occurred February 10, 1955, and she has had normal menstrual periods since then. At 16 years of age she has gained from 96 to 133 pounds and is 5 feet 5 inches tall. She leads a busy life. She has not received adrenal steroids.

*Antimetabolites** (Table 22). In the patient who has a normal or low leukocyte count and is under the age of eight or nine years, either folic acid antagonists or purine antagonists may be expected to produce a remission. In the adult and the older child responses to the purine antagonists are more likely to occur than with folic acid antagonists, although some young adults and many children also respond to the folic acid antagonists. Ellison[24] reported remissions from Methotrexate in the adults who have responded and then became resistant to Purinethol. If the peripheral leukocyte count is over 50,000, it may show a precipitous fall on Methotrexate. Therefore it may be easier to treat this patient initially with a purine antagonist. Methotrexate is given after resistance to Purinethol has occurred and as soon as the marrow shows signs of relapse.

While administering the antimetabolites, the oral mucosa is inspected daily (by the mother if the patient is being treated in the outpatient department) for ulcers, and the leukocyte and hemoglobin levels are determined daily to twice weekly. The drug is withheld if oral ulcers develop, but restarted after they have healed or if the leukocyte count drops too rapidly. Thus serious toxicity can be avoided. Excessive doses will produce severe mouth ulcers, diarrhea, and depression of the normal marrow. In some initially apparently resistant cases, however, it may be necessary to produce moderately severe toxicity, perhaps several times, before a satisfactory remission occurs, but this is usually unnecessary. Excessive toxicity will also develop if the patient's blood urea nitrogen level reflects signs of impaired renal function.

The peripheral blood picture tends to lag behind the status of the bone marrow by two or more weeks; thus during the first 10 days to 2 weeks of antimetabolite therapy, while the bone marrow may improve, the signs of leukemia as evidenced by thrombocytopenia and anemia may progress. If this is interpreted as drug toxicity and the drug withheld, there will be no possibility of producing a remission. Informing the parents that the patient may become worse before a remission occurs will lessen their apprehension during the early phase of treatment. The aim in therapy is to suppress selectively the leukemic process without impairing the survival and recovery of the normal elements

* These agents are among the most toxic which find their way into the home. It is the responsibility of the physician who prescribes them to caution the parents so that the patient is not allowed to intoxicate himself, but particularly that the normal siblings have no access to these drugs. It is recommended that only small numbers of pills be sent into the home and that the parents be required to account for every pill. If accidental ingestion occurs, determine how many pills are missing and remove any present in the stomach. Folinic acid is an excellent antidote if it is given immediately after ingestion of Methotrexate. It is not effective after the tissue damage produced by Methotrexate has occurred. The drug company that makes the preparation should also be contacted. It may be helpful to collect serum and urine for a determination of the amount absorbed.

of the bone marrow. Therefore the peripheral leukocyte count must be carefully brought down to levels of 2000 to 1000 and the drugs continued at tolerated dosage until evidence of improvement in the bone marrow occurs. Reducing the dosage of antimetabolite for maintenance therapy is unnecessary. Methotrexate should be continued at an adequate therapeutic dose or discontinued. If the patient is followed up by serial marrow determinations, when about 50 per cent of the nucleated cells are again leukemic, therapy should be resumed. If he relapses while being maintained on the drug, resistance of the leukemic cell is present, and a new type of agent should be tried. Figure 104 shows that a child may grow and develop normally while antimetabolites are being given continuously in dosages capable of producing hematologic remissions.

Since the original discovery by Farber et al.[27] that remissions could be produced regularly in children with acute leukemia by administration of the folic acid antagonists, a tremendous literature has accumulated on the experimental and clinical use of antimetabolites. The clinical experiences of numerous investigators,[7, 9] the mechanisms of action and laboratory data on experimental animals have been summarized for the folic acid antagonists[7, 9, 14, 49] and the purine analogues.[8, 13, 41]

A number of derivatives of the folic acid antagonists have been studied clinically, but none seems to have any advantage over Methotrexate. Dichloroamethopterin has been more effective than the other folic acid antagonists against mouse leukemia,[33] but has not proved more useful therapeutically than Methotrexate in leukemia in children.[31] Another form of folic acid antagonist, 2,4-diamino-5-(3′4′-dichlorophenyl)-6-methylpyrimidine, in clinical trials produced hematologic remissions, but was inferior to Methotrexate in therapeutic activity.[43]

A great variety of purine analogues have been used in leukemia in children; 6-thioguanine, 6-chloropurine and 6-methyl-mercaptopurine have the same therapeutic spectrum of action as Purinethol, whereas purine, 8-azaguanine and aminonucleoside were without therapeutic activity: 2-6-diaminopurine has a depressant effect on hematopoiesis, but did not produce a substantial degree of improvement in leukemia.[8]

Another antimetabolite, 0-diazoacetyl-L-serine (azaserine)[25] has been evaluated in neoplastic disease. It has little intrinsic activity against acute leukemia, but there is suggestive evidence that, administered in combination with Purinethol, it may prolong the response to Purinethol. This effect is so irregular, however, that there appears to be little indication for its general use.[11]

INTRATHECAL METHOTREXATE. Involvement of the nervous system with leukemia is being recognized with increasing frequency. These com-

plications may be observed when the patient is in hematologic remission on antimetabolite therapy as well as when in relapse. X-ray therapy to the skull or the vertebral column will control these complications temporarily, but it is not always satisfactory, and alopecia may be a distressing problem. Methotrexate penetrates poorly into the cerebrospinal fluid, and thus the leukemic cells may survive in their cerebral sanctuary while the disease is in remission elsewhere. The observation led to the studies on the intrathecal administration of Methotrexate in children with leukemic involvement of the central nervous system.[61]

Twenty-three children with neurologic symptoms presumably due to leukemic infiltration with leukemia have been treated with intrathecal Methotrexate. The results are summarized in Table 23. The best

TABLE 23. *Intrathecal Methotrexate in Treatment of Central Nervous System Involvement with Leukemia (23 Cases)*

MAJOR SYMPTOMS	NO. CELLS CSF ml.³ NO. CASES >1000	<1000	NUMBER DOSES MAX.	MIN.	USUAL	RESPONSE GOOD	POOR	DURATION REMISSION MONTHS RANGE	MEAN
Increased intracranial pressure	10	4	9	2	3	12	2*	8	5
Weakness of lower extremities	0	9	3	1	1	0	9	None	

* Died of intracranial hemorrhage after one dose.

results are obtained in the patient with headache, increased intracranial pressure, papilledema, vomiting, separation of the cranial sutures and a pleocytosis of the cerebrospinal fluid presumably due to meningeal infiltration. A summary of a patient's responses is shown in Figure 105. In patients with less than 1000 cells in the cerebrospinal fluid, and weakness of the extremities, no improvement was obtained in 9 cases. These patients had advanced disease, and the cause of the weakness of the extremities is not certain.

The dose of intrathecal Methotrexate is either 0.25 mg. per kilogram every second to third day or 0.5 mg. per kilogram every fourth to fifth day. Usually one additional dose is given after the cerebrospinal cell count has returned to normal. In some cases two doses are sufficient. In one patient an effort was made to control the disease in the bone marrow by this route. He received a total of 10 doses without undesirable local effect, and a partial bone marrow remission developed.

When 0.5 mg. per kilogram of the drug is injected intrathecally into anesthetized dogs, it appears in the serum and urine within 15 minutes, and the serum level rises to 0.1 gamma per milliliter and gradually falls to 0.01 gamma in 24 hours, and none

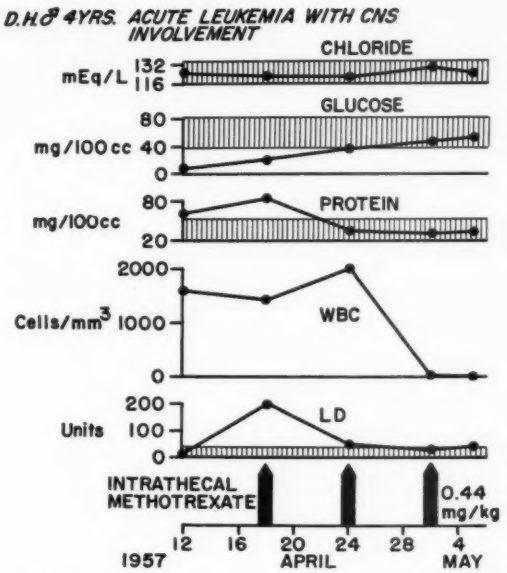


Fig. 105. Acute leukemia with central nervous system involvement responding to intrathecal Methotrexate.

This 4-year-old white boy with acute leukemia was treated with antimetabolites with a good response for 2½ years and was in a complete hematologic remission when he began to eat more than usual and gained 30 pounds in 2 months. He was found to have separation of the cranial sutures, papilledema and the cerebrospinal fluid findings shown in the chart. The morphology of the cells in the cerebrospinal fluid was that of leukemic cells, although the marrow and peripheral blood were in remission. Improvement developed after 3 doses of intrathecal Methotrexate, and the cerebrospinal fluid findings are shown. Three months later a systemic relapse occurred, and the boy died of bleeding. At autopsy leukemic infiltration of the meninges was found.

is present in 48 hours. The cerebrospinal fluid level is elevated to 1119 gammas per milliliter in 15 minutes, 2.8 gammas at 24 hours and 0.02 gamma at 72 hours. It acts as a depot to release the drug slowly into the systemic circulation.

Similar results have been found in patients.[61] During the period of intrathecal treatment oral Methotrexate should be interrupted temporarily.

If the bone marrow is relapsing on antimetabolite therapy and the patient is in poor general condition, the neurologic and the systemic disease should be treated by oral adrenal corticosteroids.

Adrenal Corticosteroids and Adrenocorticotropic Hormone (ACTH). This group of agents has a beneficial effect in about 70 to 80 per cent of the children with acute leukemia. It produces a favorable response rapidly (Table 22).

A patient with active bleeding, high fever, and in a toxic state from

the disease may show cessation of bleeding, fall in temperature and general improvement within a few hours after starting a continuous intravenous infusion of 5 per cent glucose in water containing ACTH. In a group of 21 leukemic children treated with prednisone 50 per cent of those responding did so within 8 days.[35] Twenty-two per cent showed complete and 44 per cent partial remissions.

The duration of the remission is shorter than with the antimetabolites, and for succeeding remissions higher dosages of longer duration are necessary, until the patient becomes resistant to therapy.

Marrow examinations done at one- to two-week intervals serve as a guide to steroid therapy. If remission has not occurred, the dosage of prednisone may be doubled and continued for another two weeks. When remission is obtained, the steroid should be discontinued fairly promptly. Maintenance therapy with steroids over a long time produces the undesirable Cushing's appearance shown in Figure 106, A. If they are given until complete resistance develops, they are not useful in emergency situations in later management of the disease. Prolonged use of high doses may cause a Cushing's effect with diabetes, hypertension, plethoric appearance, acne, osteoporosis and excessive weight gain. In the case of ACTH, hydrocortisone and prednisolone or prednisone in exceptionally high dosages, extracellular fluid, sodium and potassium balance must be followed carefully.

HYPERURICEMIA. The patient with a greatly elevated peripheral leukocyte count, fever, enlarged liver and spleen, nodes, and renal involvement who is started on ACTH or prednisone must be watched carefully. If the leukemic cells respond to the adrenal steroids, a single day of treatment may be sufficient to destroy a large volume of leukemic tissue, raising the serum uric acid to levels as high as 80 mg. per 100 ml. Hematuria and anuria and renal insufficiency may lead to death.[37] Figure 107 shows one patient of this type who survived when artificial renal dialysis was used.

Patients in this situation are treated with blood transfusions and parenteral fluids for the first 12 hours. When an adequate urinary flow has been established, a test dose of an adrenal corticosteroid is given. The patient is continued on intravenous fluids and the cooled urine examined for uric acid crystals. Frequent white blood cell counts and serum uric acid levels are taken and the patient examined for decreased organ size to determine when it is safe to raise the dose of the steroid to the usual therapeutic level.

NEW THERAPEUTIC METHODS. The complete remissions produced by the drugs described are satisfactory, but they are temporary, and not all patients respond to treatment. Several new methods of treatment are under investigation.

A B

Fig. 106. Cushing's effects produced by prolonged adrenocorticosteroid therapy which slowly disappeared after it had been changed to antimetabolite. A 4½-year-old girl was found to have acute leukemia in September, 1957. She received prednisone with an excellent response. The dosage was 40 mg. a day for 4 months and then 20 mg. a day for 2 months. By this time she had gained 26 pounds and had the Cushing's appearance shown in *A*. She was in leukemic relapse and had severe bone pain when she was referred to us in April, 1958. The Meticorten was gradually discontinued and antimetabolite therapy (thioguanosine, 2 mg./kg./day) started. A complete hematologic remission developed. The photograph in *B* shows her 4 months (August, 1958) after the first had been taken, illustrating the restoration of her normal appearance. She was maintained on thioguanosine for 8 months before relapse occurred. At present she is receiving Methotrexate.

There is an accelerated program for the screening of chemicals and microbiological filtrates for chemotherapeutic activity under the Cancer Chemotherapy National Service Center. New drugs are being tested at the rate of 40,000 each year against experimental animal tumors, and selected active compounds are evaluated in acute leukemia in children as well as in patients with other types of cancer.[51]

There is a program to prepare synthetic purine and pyrimidine analogues for clinical trial. Thus far 6-azauracil and several fluorinated pyrimidines have been studied, but they have not produced satisfactory therapeutic response in acute leukemia.[3, 19, 23, 30, 42, 52]

The value of total body *irradiation* in the range of 200 to 800 roentgens to the leukemic child followed by injection of isologous or homologous normal bone marrow is now undergoing clinical trial. This is

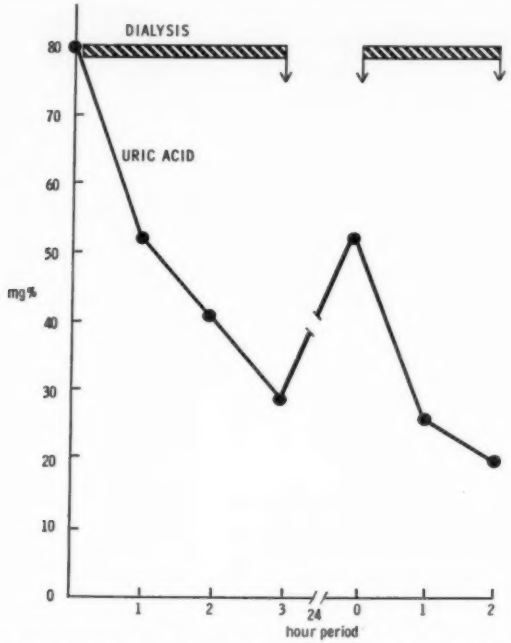


Fig. 107. Hyperuricemia as a complication in treatment of acute leukemia. This graph shows the serum uric acid levels in a patient with renal shutdown due to hyperuricemia which was treated by use of an artificial kidney.

A 7-year-old boy was operated on for abdominal lymphosarcoma and thereafter received a course of x-ray therapy to the abdomen for 21 days, during which time the abdominal tumor recurred, vomiting began, and he was referred to Memorial Center. He had a temperature of 103° F., and his abdomen was enlarged because of the tumor mass. Peripheral blood showed a hemoglobin count of 11 gm. per 100 ml. and a leukocyte count of 20,000 with 55 per cent polymorphonuclear leukocytes and 43,000 platelets. The bone marrow contained 91 per cent blast cells. Intravenous fluids were started, and during the first 8 hours 5 mg. of prednisolone were added in the infusion. The blood urea nitrogen rose from 32 to 60 mg. per 100 ml. The initial uric acid level was not taken, but 8 hours after prednisolone had been started it was 50 mg. per 100 ml. This was associated with a striking decrease in the abdominal tumor. His 8-hour urinary output was about 15 cc., and none thereafter. The steroid was discontinued, and since the uric acid rose to 80 mg. per 100 ml., the blood urea nitrogen to 131 mg., the serum phosphorus to 29 mg. and the serum potassium to 7.6 mEq. per liter, he was dialyzed for 3 hours. The uric acid decreased to 29 mg. per 100 ml. and the potassium to 4.8 mEq. per liter. At the end of 24 hours the uric acid was rising again. It was decided to increase the dose of prednisolone to 80 mg. a day in order to destroy as much of the tumor as possible, and to repeat the dialysis. After the second dialysis the steroid was discontinued and not restarted until adequate urine output was resumed. Thereafter he received Medrol, 80 mg. a day, and 6-mercaptopurine. A partial bone marrow remission developed, the abdominal tumor recurred, and 5 weeks after admission the boy died of an intestinal hemorrhage. At necropsy the kidneys showed no evidence of invasion by leukemic cells. (Graph prepared by J. Firmat, M.D., of the Physiology Service at Memorial Hospital.[29])

a difficult undertaking, and the possibility of complete success seems remote. The protective value of homologous marrow in the irradiated human host has not been proved, and if the marrow does survive, the possibility of an immune reaction due to incompatibilities between the grafted marrow and the host tissues must be anticipated. Even if all goes well technically, the maximum dose of x-rays tolerated by the host is very likely insufficient to sterilize all the leukemic cells. It is a tribute to the devotion and courage of the investigators in this field that this therapeutic approach is nevertheless under study.[28, 58]

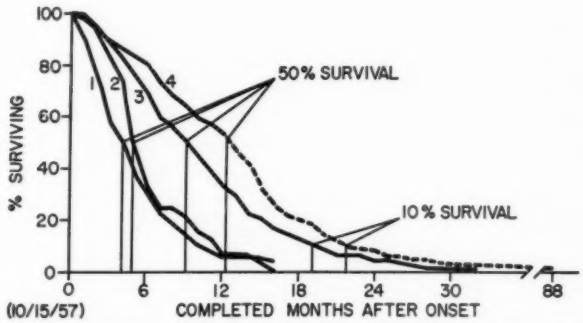


Fig. 108. Acute leukemia. Graph showing survival from onset in completed months in patients less than 15 years of age on admission. *1*, 218 cases "untreated" (reported by H. Tivey: *Pediatrics*, 10:18, 1952). *2*, 34 cases January 1, 1946, to January 1, 1948. Treatment available: nitrogen mustards. *3*, 160 cases January 1, 1948, to January 1, 1952. Treatment available: antifolics and/or steroids. *4*, 253 cases January 1, 1952, to October 15, 1956. Treatment available: antifolics, steroids, 6-mercaptopurine and azaserine.

Survivals. The results of treatment of leukemia of childhood are shown in Figure 108. For patients treated before the folic acid antagonists were first available the 50 per cent survival time was 4 to 5 months, as compared with 9.2 months when folic acid antagonists and/or adrenal corticosteroids were used and 12.5 months since 6-mercaptopurine was added.

CHRONIC GRANULOCYTIC LEUKEMIA

Clinical Characterization

Cooke[17] in a review of his cases between 1931 and 1950 found that 5 per cent of 294 cases of childhood leukemia were chronic granulocytic leukemia. The age incidence of reported cases of chronic leukemia in children spreads from 3 months to 14 years. It is pointed out, however, and this has been our experience, that the disease as it occurs in the infant under the age of two years has some special considerations.[17, 48]

Chronic granulocytic leukemia of infants appears to behave differently from the disease in older children and adults. The peripheral leukocyte count, which consists of myelocytes and promyelocytes, is usually not higher than 100,000, the spleen and liver are hard and may be greatly enlarged, and lymphadenopathy is present. These infants, in spite of erythroid activity in the marrow, are severely anemic. Megakaryocytes may be absent in the marrow, and thrombocytopenia and hemorrhagic manifestations are severe. These babies usually do poorly regardless of therapy. One of Cooke's patients, however, diagnosed at 13 months of age, was treated with irradiation and transfusions and was surviving 3 years later. Another patient, diagnosed at three months of age and treated with transfusions, x-rays to the spleen, and later with 6-mercaptopurine, died at the age of seven years. He was physically stunted and died with a picture of acute leukemia (personal communication from Olga Haller, M.D.).

The disease in the older child resembles that in the adult in signs and symptoms. There is fatigue, sweating, weakness and purpura. The spleen is greatly enlarged, the thrombocyte count is normal or elevated, and the leukocyte count is usually over 100,000. Lymphadenopathy is absent, anemia is usually present, and the child responds to conventional therapy.

Chronic granulocytic leukemia can be differentiated from acute leukemia by the large numbers of immature myeloid elements and relatively few blasts in the bone marrow, and by the predominance of myeloid cells in the peripheral blood.

Treatment

Except in the infant under two years who is not very responsive, the treatment of chronic granulocytic leukemia in children is essentially the same as in the adult. Supportive therapy with blood transfusions or antibiotics should be given if indicated. The types of agents used with examples recommended are shown in Table 24. A course of x-rays to the spleen, in small doses of 50 to 100 roentgens daily up to 200 to 400 roentgens total dose, will cause a decrease in splenomegaly; the peripheral leukocyte count will fall, the myelocytes disappear, the elevated thrombocyte count return to normal, and the hyperplastic appearance of the marrow recedes. The symptoms of fatigue and purpura disappear. The patient is not treated until the disease recurs.

If an alkylating agent is given, the peripheral leukocyte count is maintained below 20,000. Once the patient responds, the alkylating agent may be discontinued and restarted when signs of the disease recur. In many clinics an alkylating agent, Myleran, is given by mouth

as maintenance therapy.[32] Severe and fatal hematologic depression may occur from overdosage with alkylating agents. The dose of Myleran is 60 gammas per kilogram per day orally for 4 to 8 weeks if the peripheral blood does not reflect signs of hematopoietic depression. If the patient continues to do well, maintenance therapy may be given, but it is interrupted if there is any sign of hematologic depression.

TABLE 24. *Therapy of Chronic Granulocytic Leukemia*

STAGE OF DISEASE	RADIATION	CHEMOTHERAPY
Early	No therapy if no symptoms X-rays applied to spleen: 200–400 r P^{32}	Alkylating agents Purinethol Fowler's solution Urethane
Intermediate	Higher dosages of radiation to the spleen	Alkylating agents Examples: Myleran, 60 gammas/kg./day p.o. HN2, 0.4 mg./kg. i.v. (single injection) This group of agents causes slight nausea or vomiting and, in toxic doses, severe and prolonged marrow depression. The dosage should be gauged by the maintenance of normal platelet and peripheral leukocyte counts. Purine antagonists Example: Purinethol, 2.5 mg./kg./day p.o. Follow peripheral blood to determine toxicity.
Late and blastic phases	No	Purinethol Methotrexate Adrenal corticosteroids (see Acute Leukemia)

6-Mercaptopurine given at 2.5 mg. per kilogram per day continuously or intermittently may keep the disease in control for long periods of time. Hematologic depression may occur with overdosage, and on maintenance therapy, when the disease is in control, the peripheral blood should be examined at intervals of three to four weeks.

Whatever agent is used, it appears that, once resistance has developed, even though another agent is started, the response is usually poor. Eventually the disease develops a blastic marrow picture and lymphadenopathy similar to that of acute leukemia, and may respond to similar forms of treatment.

A patient treated first with x-rays to the spleen, then with Purinethol,

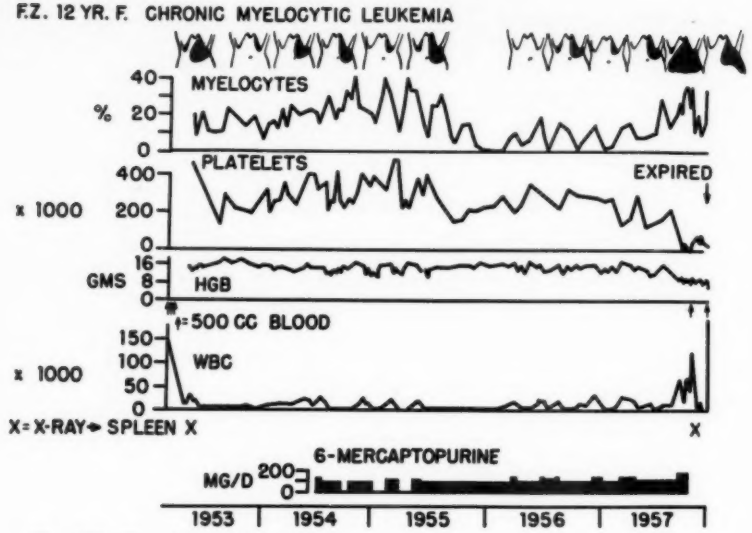


Fig. 109. Chronic granulocytic leukemia.

A 12-year-old white girl began to complain of pain in the left flank and was noted to be pale in February, 1953. On examination the physician found an enlarged spleen. She was anemic, the peripheral leukocyte count was 132,000, and it contained immature granulocytic cells. The course of her disease is shown. She received 3 blood transfusions and a total of 700 roentgens over the spleen from March 16 through April 6, 1953, with an excellent response. She was then referred to Memorial Center. The leukocyte count continued to decrease until June, 1953, when it was 7000. No therapy was given until June, 1954, when the total leukocyte count rose to 30,000 and splenomegaly recurred. 6-Mercaptopurine, 2.5 mg. per kilogram, was given with a good remission until December, 1957, when she was again anemic and splenomegaly recurred. She failed to respond to radiation to the spleen and died 5 years after the clinical onset of her disease.

had a good response for more than four years (Fig. 109). Similar results may be expected with intermittent courses of x-ray therapy to the spleen and/or interrupted courses of an alkylating agent.

HODGKIN'S DISEASE

Clinical Characterization

About 10 per cent of the cases of Hodgkin's disease occur under the age of 10 years.[36] Zellweger's[62] data suggest that the disease occurs somewhat more frequently among the children in Lebanon. Smith[54] reviewed 85 cases in the literature together with 23 of his own. In the child over the age of 10 Hodgkin's disease parallels the adult disease, but in the younger child it is more fulminating. The earliest of the signs and symptoms is usually lymphadenopathy. Later there is fever, abdominal pain, pallor, anemia, leukocytosis, fatigability, weight loss

and anorexia. Pruritus rarely, if ever, is observed in children. The liver and spleen, retroperitoneal nodes, the bones, the lungs, the pleura, the nervous system, the genitourinary system, the gastrointestinal tract and the bone marrow may become involved, with disturbances in organ function. The patient may die from cachexia or from progressive anemia due to bone marrow involvement by disease or as a result of treatment or to some overwhelming infection.

For purposes of evaluating the disease at the onset or as a guide to treatment, a clinical classification is used. This is modified from Peters[44] and Diamond.[22]

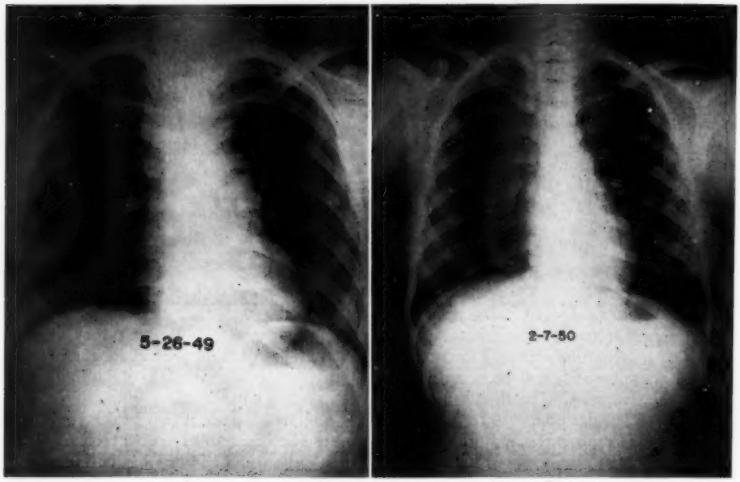
Class 0. No evidence of disease because of prior therapy.
Class I. *Localized:* The disease clinically involves a single node region or a single locus elsewhere. The patient is without constitutional symptoms or signs such as fever, anemia or fatigue.
Class II. *Regional:* The disease involves two adjacent lymph node regions (examples, cervical nodes and mediastinum or axillary nodes) and is limited to either all above the diaphragm or all below the diaphragm with or without systemic symptoms and signs.
Class III. *Generalized:* The disease extends beyond a regional classification and has constitutional systemic symptoms and signs. The bone marrow may be invaded.

Treatment

In Hodgkin's disease, as contrasted to the leukemias, there is the possibility that when the disease is localized, in a contiguous area, surgical excision and/or irradiation may possibly eradicate the disease. This is impossible to prove in an individual case because of the variable course of the disease, but Figure 110 illustrates a patient treated in this manner.

In regional disease the patient may show fever and leukocytosis which disappear after local x-ray therapy and/or chemotherapy. In the generalized disease the patients obtain temporary remissions after localized irradiation. Because of the systemic symptoms, however, HN2 (Mustargen Hydrochloride), 0.4 mg. per kilogram intravenously, or maintenance doses of one of the oral alkylating agents such as chlorambucil (Leukeran), 0.1 to 0.2 mg. per kilogram per day, may produce good relief.[5] If there is some depression of the normal leukocyte or thrombocyte count in the peripheral blood when treatment is started, the dosage must be decreased accordingly. During therapy the leukocyte and platelet counts and the patient's clinical response are guides to dosage and the continuation of treatment.

The duration of remissions resulting from treatment becomes shorter, and the bone marrow is depressed for longer periods by radiotherapy or the alkylating agents. At this stage large doses of the adrenal corticosteroids may be beneficial, particularly in the management of



A B

Fig. 110. Hodgkin's disease.

An 11-year-old white girl was noted to have a swelling of the left side of the neck in May, 1949. A diagnostic chest x-ray showed widening of the mediastinum and fullness of the left side of the neck (A). The following day a rash typical of rubella developed, and she was discharged to her home and returned in 2 weeks. At this admission the mass in the left supraclavicular area was 6 by 9 cm. and surrounded by 0.5- to 1-cm. nodes in the anterior and posterior cervical chains. The trachea was deviated to the right. An excisional biopsy of the mass in the neck and removal of a lymph node and aspiration of the main mass showed inflammatory tissue. A partial neck dissection was then carried out on June 7, 1949, and encapsulated tumor lying deep to the sternocleidomastoid and omohyoid muscles and extending beneath the left clavicle was found. Two wedges of tissue were removed. This material, 16 days after the second hospital admission, was diagnostic of Hodgkin's disease. The leukocyte count was 10,000 per cubic millimeter, the hemoglobin 12.0 gm. per 100 ml. Aside from the findings in the neck and mediastinum, there was no other evidence of disease.

The patient was treated with 0.4 mg. per kilogram of nitrogen mustard administered intravenously, followed by x-ray therapy, 2400 roentgens tumor dose to the mediastinal nodes in 7 days; 2000 roentgens tumor dose in a 12- by 9-cm. port to the left neck nodes in 6 days; and 1300 roentgens tumor dose in a 4- by 4-cm. port to the right neck nodes in 3 days. There was prompt regression of the cervical and mediastinal adenopathy. An area of induration and pigmentation of the skin persisted for 6 months. At the end of x-ray therapy the hemoglobin was depressed to 10 gm. per 100 ml., the leukocyte count to 2400 and platelets to 130,000. There was gradual return to normal values within the following months. The thoracic roentgenogram in *B* was taken 8 months after therapy.

The patient has been followed up regularly. At present she weighs 120 pounds, has no signs of recurrence of her disease, and is living a normal life.

an acquired hemolytic anemia. Antimetabolites have not been helpful in the management of Hodgkin's disease. Death usually occurs due to hematologic depression, failure to maintain adequate nutrition in view of the fever and anorexia, or secondary bacterial, fungal or viral infections due to impaired resistance.

The actinomycins, particularly actinomycins C and D, have some favorable effects in early cases of Hodgkin's disease, but rarely in the advanced disease. Thus far there is no evidence that these agents have a unique role in the management of Hodgkin's disease, although other types of actinomycins are under study.[57]

LYMPHOSARCOMA, INCLUDING RETICULUM CELL SARCOMA

Clinical Characterization

Lymphosarcomas are mainly of two types, the lymphocytic and reticulum cell sarcoma. In the former variety the normal architecture of the lymph nodes is destroyed by the small to medium-sized lymphocytic cell with malignant characteristics. There is invasion of the stromal components of the nodes and the vascular walls. The reticulum cell sarcoma is composed of larger, paler cells having a reticular appearance with normal lymphocytes present. The affected lymph nodes are enlarged, and the diagnosis is made by excision or biopsy and histologic examination. The tumor may arise as a single mass or in multiple lymph nodes simultaneously. Early the disease may be regional, but ultimately most of the lymphatic tissue is involved, and any tissues, including the bone marrow, may show an invasion as the disease process advances. The actual number of lymphosarcomas which develop a leukemic blood picture is uncertain, but the incidence is undoubtedly higher when patients are under careful observation. An incidence of 14 per cent was reported in one series[50] and 37 per cent in another.[20] The pathologist may often be unable to differentiate between lymphatic leukemia and lymphosarcoma on the histologic appearance of the nodes alone, and the bone marrow contents and clinical picture as well must be invoked for the diagnosis.

The most frequent sites of lymphosarcoma were the neck, the abdomen, retroperitoneal region and bones in a series of 27 cases that did not develop leukemia reported by Dargeon.[20] In the same series, 16 cases eventually developed a leukemic bone marrow picture; half of this group presented with mediastinal enlargement, and symptoms such as swelling, dysphagia, cough, dyspnea and pleural effusion. Fever is present if secondary infection occurs, or may be entirely absent even with extensive disease, but occurs with secondary infection.

The disease can be arrested in the localized form by early diagnosis and treatment, and Dargeon[20] has 3 of 50 patients who are surviving 4, 6 and 11 years after the initial diagnosis. The generalized disease may involve all lymphoid tissues, the liver, spleen, kidneys, lungs, brain, spinal cord and retroperitoneal tissues. A distressing complication is infiltration of the jaws with distortion of the molar teeth. In Dargeon's[20] series approximately 37 per cent of the cases of lymphosarcoma

and reticulum cell sarcoma who entered without a leukemic blood picture developed a leukemic picture within a few weeks to a few months. Some cases presenting as an acute leukemia have a long history of lymphadenopathy and undoubtedly would have been diagnosed as lymphosarcoma had a node biopsy been taken before invasion of the bone marrow. If these cases could be included, the incidence of lymphosarcoma developing into leukemia might approach 50 per cent in children.

Treatment

Prolonged survival and possible cure of lymphosarcoma in children have been reported by Dargeon.[20] One of his cases is summarized here:

S.H., a 3-year-old white boy, in March, 1954, had a rhinitis which was not relieved by antihistaminics. By July he had stertorous breathing at night, and a few days after admission was found to assume a knee-chest position during sleep. He had become more irritable and had lost 2 or 3 pounds. On examination the child was a mouth-breather, with mucus found in both nares. The soft palate was pushed forward, and a finger could palpate a mass, and if the soft palate were elevated, a large meaty mass was visualized which filled the nasopharynx. Five or 6 pieces of this tissue were removed for histologic examination. A diagnosis of lymphosarcoma was made, and one x-ray treatment of 200 roentgens was given, and the patient was referred to Memorial Center. The results of chest x-ray, skeletal survey, bone marrow aspiration, peripheral blood studies and tuberculin tests were normal or negative. He received 2.6 mg. of HN2 and x-ray therapy at 250 kilovolts (H.V.L. 2 mm. Cu) with a tumor dose of 3400 roentgens in 2 courses in 54 days to the nasopharyngeal tumor, 2200

TABLE 25. *Therapy of Hodgkin's Disease*

STAGE OF DISEASE	SURGICAL EXCISION	LOCALIZED X-RAY THERAPY	CHEMOTHERAPY
Stage I	An elective procedure	Obliterative therapy, 2000–3000 r	Only as adjuvant to irradiation or surgery: HN2, 0.4 mg./kg. i.v.
Stage II		Obliterative, 2000–3000 r	Adjuvant to irradiation: HN2, 0.4 mg./kg. i.v.
Stage III		Local palliative dosage, 600–2000 r	If hematologic status is relatively normal: Alkylating agents Examples Chlorambucil, 0.1–0.2 mg./kg./day p.o. for 21 days or until leukocytes or platelets begin to fall HN2, 0.2–0.4 mg./kg. i.v.
Marrow depression due to disease or after irradiation or chemical treatment			If hematologic depression is present: Prednisone, 10–50 mg./day

roentgens in 20 days to the cervical nodes. He also had gold seeds totalling 3.00 mc inserted into a node in the left midspinal accessory chain. His symptoms cleared slowly during the course of therapy. Since 1954 he was given interrupted courses of Methotrexate. It has been 4½ years since the clinical onset of the disease, and there is no evidence of recurrence.

Lymphosarcoma may be classified also as localized, regional or systemic, and the therapy for each type is similar to that for Hodgkin's disease (Table 25). If the disease invades the bone marrow and produces a leukemic picture, therapy becomes identical with that for acute leukemia.

SUMMARY

Some of the practical details in the management of leukemia and lymphoma are reviewed in this report. The use of the adrenal steroids, folic acid antagonists and 6-mercaptopurine in acute leukemia has caused a definite prolongation of life, but the leukemic process ultimately becomes resistant. The use of intrathecal Methotrexate, a folic acid antagonist, has successfully relieved neurologic complications due to leukemic infiltration of the central nervous system. Other drugs and procedures under study are described, but heretofore they have not appreciably modified the course of acute leukemia.

Chronic granulocytic leukemia represents only about 5 per cent of the leukemias in children and generally responds, as in adults, to radiotherapy to the spleen, radioactive phosphorus, the alkylating agents and 6-mercaptopurine.

In localized Hodgkin's disease and lymphosarcoma, surgical excision, when feasible, and intensive radiotherapy, sometimes in combination with an alkylating agent, are recommended. In some of these cases the disease has been arrested for many years. In the disseminated disease local radiotherapy and some form of alkylating agent may relieve the systemic manifestations of the disease.

Lymphosarcoma in children frequently evolves into a leukemic phase, and at this time it is treated as an acute leukemia.

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